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(71) Applicant (for all designated States except US):
WARNER-LAMBERT COMPANY [US/US]; 201
Tabor Road, Morris Plains, NJ 07950 (US).

(72) Inventor; and

(75) Inventor/Applicant (for US only): **BOCAN, Thomas,
Michael, Andrew** [US/US]; 4954 High Meadow Lane,
Ann Arbor, MI 48103 (US).

(74) Agents: **FEDERMAN, Evan, J.**; Warner-Lambert Com-
pany, 201 Tabor Road, Morris Plains, NJ 07950 et al. (US).

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(54) Title: PREVENTION OF PLAQUE RUPTURE BY ACAT INHIBITORS

(57) Abstract: This invention is the administration of an ACAT inhibitor to prevent monocyte-macrophase accumulation and MMP expression in atherosclerotic lesions. Further, this invention relates to methods of inhibiting destabilization and/or rupture of atherosclerotic plaques and treatment of unstable angina.



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PREVENTION OF PLAQUE RUPTURE BY ACAT INHIBITORS

BACKGROUND OF THE INVENTION

Compounds that inhibit acyl-coenzyme A:cholesterol acyltransferase are known as ACAT inhibitors. Certain ACAT inhibitors and the methods for
5 preparing them are taught in United States Patent 5,491,172 and its divisional 5,633,287, which are hereby incorporated by reference. The use of the compounds taught is the treatment of hypercholesterolemia and atherosclerosis.

United States Patent 5,441,975 teaches ACAT inhibitors, especially
10 N-[2,6-Bis(1-methylethyl)phenyl]-2-(2-dodecyl-2*H*-tetrazol-5-yl)-2-phenyl- acetamide. This and other United States Patents in the same patent family—5,646,170; 5,693,657; and 5,366,987—are hereby incorporated by reference. The use of the compounds is treatment of hypercholesterolemia and atherosclerosis.

PCT/US99/13948 filed June 18, 1999, teaches coadministration of ACAT
15 and MMP inhibitors for the reduction of both macrophage and smooth muscle cell components of atherosclerotic lesions. The patent application is hereby incorporated by reference. The application teaches methods of preventing plaque rupture and promoting lesion regression.

None of these references disclose the use of an ACAT inhibitor alone to
20 reduce monocyte-macrophage accumulation and MMP expression in atherosclerotic plaques.

An integral process in the pathogenesis of atherosclerosis is the cholesteryl ester (CE) enrichment of the arterial wall. Cholesteryl ester enrichment can occur by passive influx and extracellular deposition of plasma lipoproteins, active
25 cellular metabolism, and active intracellular storage. In man, arterial CE content increases from approximately 2% to 50% of total vessel lipid over 70 years (Small D., Arteriosclerosis, 1988;8:103-129) with a change in the cholesteryl oleate/linoleate ratio from 0.8 to 2.9 (Smith E.B., Evans P.H. and Downham M.D., J. Atheroscler. Res., 1967;7:171-186). The change in fatty acyl pattern is a
30 reflection of a change in the relative amounts of lipoprotein-derived CE,

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cholesteryl linoleate, and ACAT-derived cholesteryl oleate (Smith E.B., Evans P.H. and Downham M.D., J. Atheroscler. Res., 1967;7:171-186). Brown and Goldstein have shown that in the 2 compartment model of cholesteryl ester cycling in the macrophage, lipoprotein-derived cholesteryl linoleate is hydrolyzed and the free cholesterol is reesterified with oleoyl-CoA by ACAT to form intracellular cholesteryl oleate enriched lipid droplets (Brown M.S. and Goldstein J.L., Ann. Rev. Biochem., 1983;52:223-261). Concomitant with the changes in CE content and fatty acyl pattern is the influx of monocyte-macrophages and smooth muscle cells (Haust M.D. in: Moore S., ed., Vascular Injury and Atherosclerosis, New York: Marcel Dekker, 1981;1-23). Thus, under conditions of excessive cholesterol accumulation in the vascular wall, acyl-CoA:cholesterol O-acyltransferase (ACAT), a primary enzyme responsible for cholesterol esterification, appears responsible for the generation of the hallmark of atherosclerosis, namely, the monocyte-macrophage foam cell.

Given the involvement of ACAT in atherosclerotic lesion development and macrophage foam cell formation, inhibitors of ACAT have been evaluated for their antiatherosclerotic activity. Such agents have been shown to effectively reduce lesion development to varying degrees. However, in almost every study the interpretation of the data was confounded by changes in plasma total cholesterol [(i) Krause B.R. and Bocan T.M.A., in: Ruffolo R.R. and Hollinger M.A., eds. Inflammation: Mediators and Pathways, 1995;173-198 (ii) Krause B.R., Sliskovic D.R. and Bocan T.M.A., Exp. Opin. Invest. Drugs, 1995;4:353-387 (iii) Roth B.D., Drug Discovery Today, 1998;3:19-25 (iv) Bocan T.M.A. Curr. Pharm. Design, 1998;4:39-53]. When plasma total cholesterol levels were unaltered by drug administration and systemic levels of drug were achieved, rather striking reductions in lesion extent, cholesteryl ester enrichment and macrophage foam cell involvement were noted (Bocan T.M.A., Bak Mueller S., Uhlendorf P.D., Newton R.S. and Krause B.R., Arterioscler. Thromb., 1991;11:1830-1843).

In the studies cited above, the various ACAT inhibitors were administered in a cholesterol-containing diet, and shown to limit the development of the macrophage enriched fatty streak or fibrofoamy lesions. In contrast to the previous cholesterol-fed animal studies, we have evaluated the effect of the ACAT inhibitor, sulfamic acid, [[2,4,6-tris(1-methylethyl)phenyl]acetyl-2,6-bis(1-

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methylethyl)phenyl ester] (hereinafter Avasimibe) in a model in which advanced fibrous plaque-like lesions develop. In order to develop advanced atherosclerotic lesions and limit the effect of plasma cholesterol lowering on changes in lesion endpoints, rabbits were switched from a cholesterol/fat diet to a chow/fat diet prior to administration of sulfamic acid, [[2,4,6-tris(1-methylethyl)phenyl]acetyl-2,6-bis(1-methylethyl)phenyl ester. Previous studies indicate that, in rabbits, reductions in plasma cholesterol levels tend to result in an advancement of atherosclerotic lesions rather than regression of atherosclerosis [(i) Constantinides P., Booth J. and Carlson G., Arch. Pathol., 1960;70:80-92 (ii) Constantinides P., J. Atheroscler. Res., 1961;1:374-385].

Monocyte-macrophage foam cells have recently been implicated in atherosclerotic lesion destabilization and rupture (Galis Z.S., Sukhova G.K., Kranzhoefer R., Clark S. and Libby P., Proc. Natl. Acad. Sci. USA, 1995;92:402-406). With atherosclerotic lesion development there is an increase in the expression of matrix metalloproteinase (MMP-1, MMP-3, MMP-7 and MMP-9 [(i) Galis Z.S., Sukhova G.K., Kranzhoefer R., Clark S. and Libby P., Proc. Natl. Acad. Sci. USA, 1995;92:402-406 (ii) Galis Z.S., Sukhova G.K., Lark M.W. and Libby P., J. Clin. Invest., 1994;94:2493-2503 (iii) Nikkari S.T., O'Brien K.D., Ferguson M., Hatsukami T., Welgus H.G., Alpers C.E., and Clowes A.W., Circulation, 1995;92:1398-1408 (iv) Halpert I., Sires U.I., Roby J.D., Potter-Perigo S., Wight T.N., Shapiro S.D., Welgus H.G., Wickline S.A., and Parks W.C., Proc. Natl. Acad. Sci. USA, 1996;93:9748-9753 (v) Brown D.L., Hibbs M.S., Kearney M., Loushin C., and Isner J.M., Circulation, 1995;91:2125-2131]. Specifically, both MMP-1 and MMP-7 have been identified in macrophage-rich regions of human carotid lesions [(i) Galis Z.S., Sukhova G.K., Kranzhoefer R., Clark S., and Libby P., Proc. Natl. Acad. Sci. USA, 1995;92:402-406 (ii) Nikkari S.T., O'Brien K.D., Ferguson M., Hatsukami T., Welgus H.G., Alpers C.E., and Clowes A.W., Circulation, 1995;92:1398-1408]. MMP-9 has been seen in atherectomy specimens from individuals with unstable angina (Brown D.L., Hibbs M.S., Kearney M., Loushin C. and Isner J.M., Circulation, 1995;91:2125-2131) and associated with macrophage-rich regions of lesions obtained at surgery or autopsy [(i) Galis Z.S., Sukhova G.K., Kranzhoefer R., Clark S., and Libby P., Proc. Natl. Acad. Sci. USA, 1995;92:402-406 (ii) Galis

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Z.S., Sukhova G.K. Lark M.W., and Libby P., J. Clin. Invest., 1994;94:2493-2503]. In addition, MMPs have been shown to be catalytically active when evaluated by gelatin or casein zymography and both the gelatinolytic and caseinolytic activity has been localized to the shoulders of atherosclerotic lesions in areas of monocyte-macrophage accumulation (Galis Z.S., Sukhova G.K., Lark M.W., and Libby P., J. Clin. Invest., 1994;94:2493-2503).

We have now discovered a surprising result. The administration of an ACAT inhibitor alone is sufficient to reduce monocyte-macrophage accumulation in atherosclerotic lesions in normal-fed mammals. A further surprising and beneficial result of the invention is that administration of an ACAT inhibitor alone is sufficient to reduce MMP expression in atherosclerotic lesions in the absence of an MMP inhibitor.

This invention provides methods of treating atherosclerosis in a mammal, particularly a human, comprising administration of a therapeutically effective amount of an ACAT inhibitor sufficient to inhibit the accumulation of monocyte-macrophages and reduce expression of matrix metalloproteinases in atherosclerotic lesions.

Further, the invention provides methods for preventing destabilization and/or rupture of atherosclerotic lesions or plaques.

Still further, the invention provides a method of treating unstable angina.

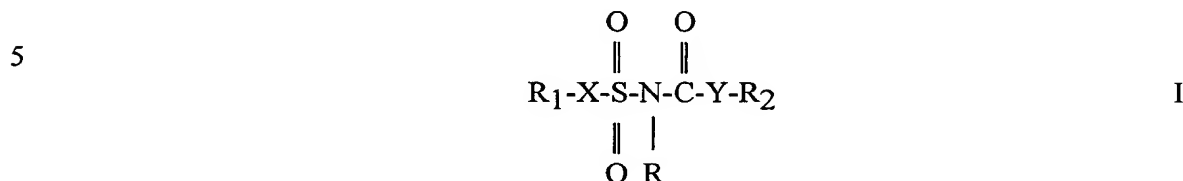
SUMMARY OF THE INVENTION

This invention provides methods of treating atherosclerosis comprising administration of an ACAT inhibitor. More particularly, the invention provides methods of inhibiting the accumulation of monocyte-macrophages in atherosclerotic lesions in a mammal, particularly a human, by administering a therapeutically effective amount of an ACAT inhibitor. The invention also provides methods for preventing destabilization and/or rupture of atherosclerotic lesions or plaques.

Certain ACAT inhibitors suitable for administration and their pharmaceutical compositions are disclosed.

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The present invention is directed to new methods of use of an ACAT inhibitor. Further, the present invention is directed to methods of use of compounds of formula



or a pharmaceutically acceptable salt thereof wherein:

- 10 X and Y are selected from oxygen, sulfur and (CR'R'') wherein n is an integer of from 1 to 4 and R' and R'' are each independently hydrogen, C₁-C₆ alkyl, C₁-C₆ alkoxy, halogen, hydroxy, C₂-C₆ acyloxy, C₃-C₁₀ cycloalkyl, phenyl optionally substituted or R' and R'' together form a C₃-C₁₀ cycloalkyl or a carbonyl;
- 15 R is hydrogen, a straight or branched alkyl of from 1 to 8 carbon atoms or benzyl; R₁ and R₂ are each independently selected from
- (a) phenyl or phenoxy each of which is unsubstituted or is substituted with 1 to 5 substituents selected from
- 20 phenyl,
an alkyl group having from 1 to 6 carbon atoms and which is straight or branched,
an alkoxy group having from 1 to 6 carbon atoms and which is straight or branched;
- 25 phenoxy,
hydroxy,
fluorine,
chlorine,
bromine,
nitro,
30 trifluoromethyl,
-COOH,

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-COOalkyl wherein alkyl has from 1 to 4 carbon atoms and is straight or branched,

-(CH₂)_pNR₃R₄ wherein p is zero or 1, and each of R₃ and R₄ is selected from hydrogen or a straight or branched alkyl group having 1 to 4 carbon atoms;

5

(b) 1- or 2-naphthyl unsubstituted or substituted with from 1 to 3 substituents selected from

phenyl,

an alkyl group having from 1 to 6 carbon atoms and which is straight or branched,

10

an alkoxy group having from 1 to 6 carbon atoms and which is straight or branched;

hydroxy,

phenoxy,

15

fluorine,

chlorine,

bromine,

nitro,

trifluoromethyl,

20

-COOH,

-COOalkyl wherein alkyl has from 1 to 4 carbon atoms and is straight or branched,

-(CH₂)_pNR₃R₄ wherein p, R₃ and R₄ have the meanings defined above;

25

(c) arylalkyl;

(d) a straight or branched alkyl chain having from 1 to 20 carbon atoms and which is saturated or contains from 1 to 3 double bonds; or

(e) adamantyl or a cycloalkyl group wherein the cycloalkyl moiety has from 3 to 10 carbon atoms.

30

Preferred compounds of the instant invention are those of Formula I: wherein R₁ is phenyl or is phenyl disubstituted in the 2,6-positions,

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wherein R₂ is phenyl or is phenyl disubstituted in the 2,6-positions,

wherein each of R₁ and R₂ is phenyl,

wherein each phenyl is disubstituted in the 2,6-position,

wherein R₁ is phenyl disubstituted in the 2,6-positions and R₂ is phenyl

5 trisubstituted in the 2,4,6-positions,

wherein R₁ is 2,6-bis(1-methylethyl)phenyl and R₂ is

2,6-bis(1-methylethyl)phenyl or 2,4,6-tris(1-methylethyl)phenyl,

wherein R₁ and R₂ are independently selected from substituted phenyl, or



wherein t and w are independently an integer of from 0 to 4 with the proviso that

15 the sum of t and w is not greater than 5; R₅ and R₆ are each independently selected from hydrogen or alkyl having from 1 to 6 carbon atoms, or when R₅ is hydrogen, R₆ can be selected from the groups defined for R₇; and R₇ is phenyl or phenyl substituted with from 1 to 3 substituents selected from a straight or branched alkyl group having from 1 to 6 carbon atoms, 20 straight or branched alkoxy group having from 1 to 6 carbon atoms, phenoxy, hydroxy, fluorine, chlorine, bromine, nitro, trifluoromethyl, -COOH, -COOalkyl, wherein alkyl has from 1 to 4 carbon atoms, or -(CH₂)_pNR₃R₄ wherein substituted phenyl p, R₃ and R₄ have the meanings as defined above.

25 Another preferred embodiment are compounds of Formula I wherein:

X is oxygen, sulfur or (CR'R'')_n;

Y is oxygen, sulfur or (CR'R'')_n, with the proviso that at least one of X or Y is

(CR'R'')_n wherein n is an integer of from 1 to 4 and R' and R'' are each

independently hydrogen, straight or branched alkyl of from 1 to 6 carbons,

30 optionally substituted phenyl, halogen, hydroxy, C₁-C₆ alkoxy, C₂-C₆

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acyloxy, C₃-C₁₀ cycloalkyl, or R' and R'' are taken together with the carbon atom to which they are attached form a carbonyl or a cycloalkyl group of from 3 to 10 carbons;

R is hydrogen;

5 R₁ is optionally substituted phenyl, straight or branched alkyl of from 4 to 10 carbon atoms, cycloalkyl of from 3 to 10 carbon atoms;

R₂ is optionally substituted phenyl, straight or branched alkyl of from 4 to 10 carbon atoms, cycloalkyl of from 3 to 10 carbon atoms, optionally substituted phenoxy; with the proviso that R₁ is optionally substituted
10 phenoxy only if X is (CR'R'')_n and R₂ is optionally substituted phenoxy only if Y is (CR'R'')_n, and with the further proviso that at least one of R₁ and R₂ is optionally substituted phenyl or phenoxy.

Another preferred embodiment are compounds of Formula I wherein:

R₁ and R₂ are independently selected from substituted phenyl, straight or
15 branched alkyl of from 4 to 10 carbon atoms, cycloalkyl of from 3 to 10 carbon atoms or substituted phenoxy;

X is oxygen;

Y is (CR'R'')_n; and

R is hydrogen

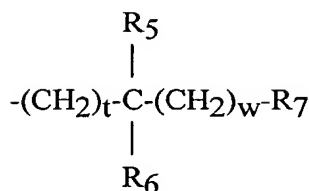
20 wherein n is an integer of 1 or 2, and substituted phenyl, R', and R'' have the meanings as defined above, and with the proviso that R₁ is optionally substituted phenoxy only if X is (CR'R'')_n and R₂ is optionally substituted phenoxy only if Y is (CR'R'')_n, and with the further proviso that at least one of R₁ and R₂ is optionally substituted phenyl or phenoxy.

25 Another preferred embodiment are compounds of Formula I wherein:

R₁ is optionally substituted phenyl;

R₂ is selected from substituted phenyl, substituted phenoxy, or

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5

wherein t and w are independently an integer of from 0 to 4 with the proviso that the sum of t and w is not greater than 5; R₅ and R₆ are each independently selected from hydrogen or alkyl having from 1 to 6 carbon atoms, or when R₅ is hydrogen, R₆ can be selected from the groups defined for R₇; and

10 R₇ is phenyl or phenyl substituted with from 1 to 3 substituents selected from a straight or branched alkyl group having from 1 to 6 carbon atoms, straight or branched alkoxy group having from 1 to 6 carbon atoms, phenoxy, hydroxy, fluorine, chlorine, bromine, nitro, trifluoromethyl, -COOH, -COOalkyl, wherein alkyl has from 1 to 4 carbon atoms, or

15 $-(CH_2)_pNR_3R_4$;

X is oxygen;

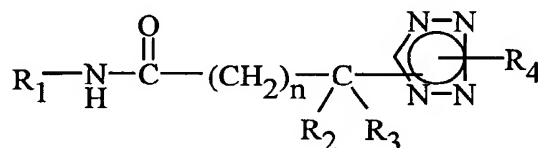
Y is $(CR'R'')_n$; and

R is hydrogen

wherein n is an integer of 1 or 2, and substituted phenyl, p, R₃, R₄, R', and R''

20 have the meanings as defined above.

Further, the present invention is directed to methods of use of compounds of formula



II

wherein n is 0, 1 or 2;

25 wherein R₁ is selected from

- (a) phenyl which is unsubstituted or is substituted with from 1 to 3 substituents selected from:

alkyl having from 1 to 4 carbon atoms and which is straight or branched,

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alkoxy having from 1 to 3 carbon atoms and which is
straight or branched,

alkylthio having from 1 to 3 carbon atoms and which is
straight or branched,

5

hydroxy,

phenyl,

fluorine,

chlorine,

bromine,

10

nitro,

cyano,

trifluoromethyl,

-COOH,

-COOalkyl wherein alkyl has from 1 to 4 carbon atoms and
which is straight or branched,

15

$-(CH_2)_mNR_5R_6$ wherein m is zero or 1, and each of R_5
and R_6 is hydrogen or a straight or branched alkyl
group having 1 to 4 carbon atoms;

(b) 1- or 2-naphthyl which is unsubstituted or substituted with 1 to
3 substituents selected from:

20

alkyl having from 1 to 4 carbon atoms and which is straight
or branched,

alkoxy having from 1 to 3 carbon atoms and which is
straight or branched,

25

hydroxy,

fluorine,

chlorine,

bromine,

nitro,

30

cyano,

trifluoromethyl,

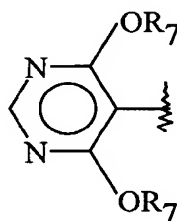
-COOH,

-11-

-COOalkyl wherein alkyl has from 1 to 4 carbon atoms and is straight or branched,

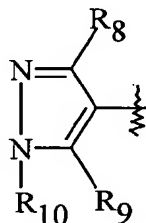
-(CH₂)_mNR₅R₆ wherein m, R₅, and R₆ have the meanings defined above;

5 (c) the group



wherein R₇ is a lower alkyl group having from 1 to 3 carbon atoms and is straight or branched;

(d) the group



10

wherein R₈ and R₉ are straight or branched alkyl having from 1 to 4 carbon atoms or phenyl, and R₁₀ is a straight or branched hydrocarbon group having from 1 to 18 carbon atoms which is saturated or is unsaturated containing 1 double bond or 2 nonadjacent double bonds; phenyl; phenyl substituted with from 1 to 3 substituents selected from straight or branched alkyl having 1 to 4 carbon atoms, straight or branched alkoxy having from 1 to 3 carbon atoms, hydroxy, fluorine, chlorine, bromine, nitro, cyano, trifluoromethyl, -COOH, -COOalkyl wherein alkyl has from 1 to 4 carbon atoms and is straight or branched or -(CH₂)_mNR₅R₆ wherein m, R₅, and R₆ are as defined above; or a heteroaryl group selected from 2-, 3-, or 4-pyridyl, 2-, 4-, or 5-pyrimidinyl, 2- or 3-pyrazinyl, 2-, 3-,

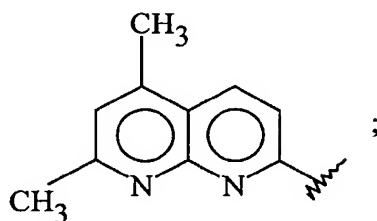
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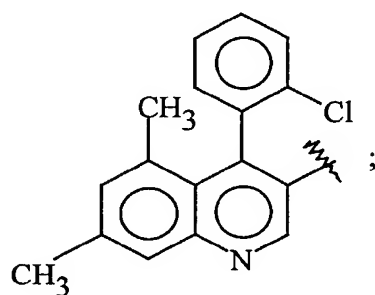
4-, 5-, 6-, 7-, or 8-quinolinyl, or 3- or 4-pyridazinyl and the N-oxides thereof;

(e) the group .



5

(f) the group



(g) a straight or branched hydrocarbon group having from 1 to 18 carbon atoms which is saturated or is unsaturated containing 1 double bond or 2 nonadjacent double bonds;

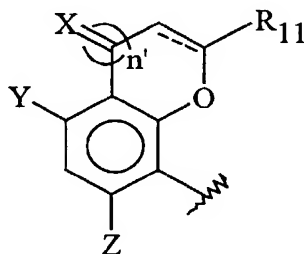
10

(h) a cycloalkyl group having from 3 to 8 carbon atoms;

(i) a heteroaryl group selected from 2-, 3-, or 4-pyridyl which is unsubstituted or substituted with an alkyl group having from 1 to 4 carbon atoms or 2-, 4-, or 5-pyrimidinyl, and the N-oxides thereof;

15

(j) the group



wherein --- denotes a single or double bond; Y and Z are each independently hydrogen, a straight or branched alkyl group

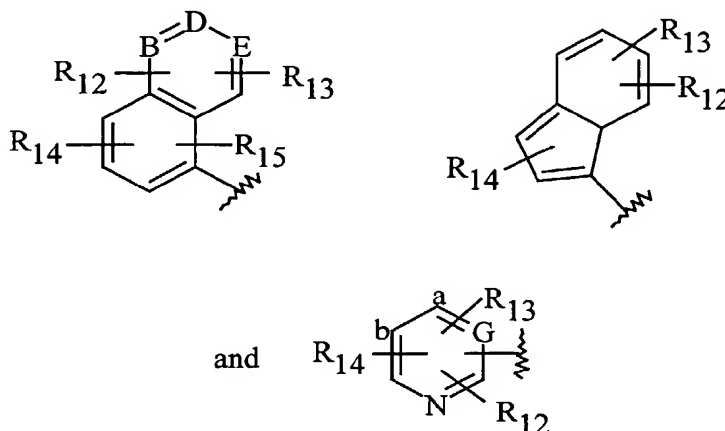
-13-

of 1 to 4 carbon atoms, an alkoxy group of 1 to 3 carbon atoms or halogen;

X is oxygen or 2 hydrogen atoms;

R₁₁ is hydrogen or a straight or branched alkyl group of 1 to 4 carbon atoms, and n' is zero or 1; or

(k) is selected from the group



wherein R₁₂, R₁₃, R₁₄, and R₁₅ are each independently hydrogen, halogen, a straight or branched alkyl group of 1 to 4 carbon atoms, an alkoxy group of 1 to 3 carbon atoms, and alkylthio group of 1 to 3 carbon atoms, cycloalkylthio of 5 to 7 carbon atoms, phenylalkylthio in which the alkylene is from 1 to 4 carbon atoms, substituted phenylthio, heteroarylthio, or heteroaryloxy; and B, D, E, and G are nitrogen or carbon where one or more of B, D, and E is nitrogen; with the proviso that when G = nitrogen the group is attached to the nitrogen atom of Formula I at the 4- or 5-position of the pyrimidine ring (a or b);

wherein R₂ and R₃ are the same or different and are selected from:

- (a) hydrogen, halogen or one of R₂ or R₃ is hydroxy;
- (b) a straight or branched alkyl group having from 1 to 12 carbon atoms, or a cycloalkyl group having from 3 to 8 carbon atoms;

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- 5 (c) a phenyl or phenylalkyl group where the alkylene is from 1 to 4 carbon atoms and which the phenyl ring unsubstituted or substituted with from 1 to 3 substituents selected from straight or branched alkyl having from 1 to 4 carbon atoms, straight or branched alkoxy having from 1 to 4 carbon atoms, alkythio, straight or branched having 1 to 4 carbon atoms, hydroxy, fluorine, chlorine, bromine, trifluoromethyl, cyano, nitro, phenyl, or
- 10 $(\text{CH}_2)_m\text{NR}_5\text{R}_6$ wherein m, R_5 , and R_6 have the meanings defined above;
- (d) a straight or branched alkenyl group having from 2 to 6 carbon atoms; or
- 15 (e) R_2 and R_3 taken together with the carbon atom to which they are attached form an alkylidene group of 1 to 4 carbon atoms, a benzylidene group, or a cycloalkyl group having from 3 to 7 carbon atoms; or
- 20 (f) when R_2 is hydrogen, F, alkyl of C_{1-12} atoms, R_3 is a heteroaryl selected from a 5- or 6-membered monocyclic or fused bicyclic group containing at least 1 to 4 heteroatoms in at least one ring, said heteroatoms being nitrogen, oxygen, or sulfur and combinations thereof, said heteroaryl group being
- 25 unsubstituted or substituted with an alkyl group having from 1 to 4 carbon atoms and the N-oxides thereof;
- 30 (g) 1- or 2-naphthyl which is unsubstituted or substituted with 1 to 3 substituents selected from: alkyl having from 1 to 4 carbon atoms and which is straight or branched,

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alkoxy having from 1 to 3 carbon atoms and which
is straight or branched;

wherein R₄ is a straight or branched hydrocarbon chain having
from 1 to 20 carbon atoms and is saturated or is unsaturated
and has 1 double bond or has 2 nonadjacent double bonds
or is alkylthio having 1 to 20 carbon atoms and is saturated;
or a pharmaceutically acceptable salt or individual
enantiomeric isomer thereof.

Preferred compounds of Formula II are those:

wherein: R₄ is in the 2-position of the tetrazole ring,
wherein: n is 0;
wherein: R₄ is straight or branched alkyl containing from 8 to 18 carbon atoms,
wherein: one of R₂ or R₃ is optionally substituted phenyl,
wherein R₁ is optionally substituted phenyl,
wherein R₁ is phenyl optionally disubstituted in the 2,6-positions,
wherein R₁ is phenyl optionally trisubstituted in the 2,4,6-positions.

Another preferred embodiment of compounds of Formula II is wherein:

R₁ is optionally substituted phenyl;
R₂ and R₃ are each independently hydrogen, cycloalkyl containing from 3 to
8 carbon atoms, optionally substituted phenyl or optionally substituted
phenylalkyl wherein the alkylene diradical is from 1 to 4 carbon atoms;
R₄ is a straight or branched alkyl containing from 8 to 18 carbon atoms and is
attached in the 2-position of the tetrazole ring; and
n is 0 or 1.

Another preferred embodiment of compounds of Formula II is wherein:

R₁ is phenyl disubstituted in the 2,6-positions or trisubstituted in the
2,4,6-positions;
R₂ and R₃ are each independently hydrogen or optionally substituted phenyl;
R₄ is a straight or branched alkyl containing from 8 to 18 carbon atoms and is
attached in the 2-position of the tetrazole ring; and
n is 0.

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BRIEF DESCRIPTION OF DRAWINGS

Figure 1 is a gelatin zymography of MMP-2 and -9 and a casein zymography of MMP-1 or -3 after treatment with avasimibe.

5 Figure 2 is a line graph with error bars showing mean plasma total cholesterol levels over the time course of the study.

Figure 3 is a bar graph showing mean plasma cholesterol exposure during the final 7-week treatment phase of the study.

Figure 4 is a gelatin zymography showing MMP-2 and -9 expression in the aortic arch of hypercholesterolemic rabbits treated with 25 mg/kg of avasimibe.

10 Figure 5 is a casein zymography showing MMP-1 or -3 expression in the aortic arch of hypercholesterolemic rabbits treated with 25 mg/kg of avasimibe.

Figure 6 is a bar graph showing the density of the various MMP zymogen bands.

15 Figure 7 is a Northern blot of MMP-2 mRNA expression in the aortic arch of progression control and avasimibe-treated animals.

Figure 8 is a Northern blot of MMP-9 mRNA expression in the aortic arch of progression control and avasimibe-treated animals.

Figure 9 is a Northern blot of TIMP-1 mRNA expression in the aortic arch of progression control and avasimibe-treated animals.

20 Figure 10 is a Northern blot of TIMP-2 mRNA expression in the aortic arch of progression control and avasimibe-treated animals.

Figure 11 is a bar graph depicting a morphometric evaluation of the extent of atherosclerosis within the thoracic aorta and the cross-sectional lesion and macrophage area within the aortic arch.

25 Figure 12 is a bar graph depicting a morphometric evaluation of the iliac-femoral cross-section lesion and macrophage area.

DETAILED DESCRIPTION OF THE INVENTION

Administration of an ACAT inhibitor can inhibit development and destabilization of atherosclerotic lesions or plaques. ACAT inhibitors have been

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shown to reduce the accumulation of monocyte-macrophages within atherosclerotic lesions of cholesterol-fed rabbits. In addition, monocyte-macrophages have been reported to secrete such matrix metalloproteinases as MMP-7 and -9 while smooth muscle cells are noted to secrete MMP-1, -2, and -3. Inhibition of ACAT while directly reducing the accumulation of lipid-filled monocyte-macrophages will decrease a substantial source of MMPs in atherosclerotic lesions. Surprisingly, administration of an ACAT inhibitor alone will inhibit cellular accumulation and development of atherosclerotic lesions as well as prevent destabilization and/or rupture of mature and developing lesions by reducing the number of lipid-filled monocyte-macrophages, a source of the matrix-degrading MMPs.

The method is practiced by administering a chemical compound effective in inhibiting the biological activity of the enzyme acyl-coenzyme A:cholesterol acyltransferase or ACAT. The numerous compounds known as ACAT inhibitors are useful in the practice of this invention. An "ACAT inhibitor" as used herein is any chemical compound that inhibits by at least 5 percent the catalytic activity of the enzyme ACAT at an inhibitor concentration of $\leq 1000 \mu\text{M}$.

Illustrative examples of a straight or branched alkyl group or radical having from 1 to 3 carbon atoms, also known as a $\text{C}_1\text{-C}_3$ alkyl, include methyl, ethyl, 1-propyl, and 2-propyl.

Illustrative examples of a straight or branched alkyl group or radical having from 1 to 4 carbon atoms, also known as a $\text{C}_1\text{-C}_4$ alkyl, include groups defined for C_1 to C_3 alkyl and 1-butyl, 2-butyl, 2-methyl-1-propyl, and 1,1-dimethylethyl.

Illustrative examples of a straight or branched alkyl group or radical having from 1 to 6 carbon atoms, also known as a $\text{C}_1\text{-C}_6$ alkyl, include groups defined for C_1 to C_4 alkyl and 1-pentyl, 2-pentyl, 3-pentyl, 2,2-dimethylpropyl, 1-hexyl, 2-hexyl, 3-hexyl, and 4-methyl-1-pentyl.

Illustrative examples of a straight or branched alkyl group or radical having from 1 to 8 carbon atoms, also known as a $\text{C}_1\text{-C}_8$ alkyl, include groups defined for C_1 to C_6 alkyl and 1-heptyl, 2-heptyl, 3-heptyl, 4-heptyl, 5-methyl-1-

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hexyl, 1-octyl, 2-octyl, 3-octyl, 4-octyl, 6-methyl-1-heptyl, and 5,5-dimethylhexyl.

Illustrative examples of a straight or branched alkyl group or radical having from 4 to 10 carbon atoms, also known as a C₄-C₁₀ alkyl, include 1-butyl, 2-butyl, 2-methyl-1-propyl, 1,1-dimethylethyl, 1-pentyl, 2-pentyl, 3-pentyl, 2,2-dimethylpropyl, 1-hexyl, 2-hexyl, 3-hexyl, 4-methyl-1-pentyl, 1-heptyl, 2-heptyl, 3-heptyl, 4-heptyl, 5-methyl-1-hexyl, 1-octyl, 2-octyl, 3-octyl, 4-octyl, 6-methyl-1-heptyl, 5,5-dimethylhexyl, 1-nonyl, 2-nonyl, 1-decyl, and 2-decyl.

Illustrative examples of a straight or branched alkyl group or radical having from 1 to 12 carbon atoms, also known as a C₁-C₁₂ alkyl, include groups defined for C₁-C₈ alkyl and 1-nonyl, 2-nonyl, 1-decyl, 2-decyl, 1-undecyl, 2-undecyl, 1-dodecyl, and 2-dodecyl.

Illustrative examples of a straight or branched alkyl group or radical having from 1 to 18 carbon atoms, also known as a C₁-C₁₈ alkyl, include groups defined for C₁ to C₁₂ alkyl and 1-tridecyl, 1-tetradecyl, 1-pentadecyl, 1-hexadecyl, 1-heptadecyl, and 1-octadecyl.

Illustrative examples of a straight or branched alkyl group or radical having from 8 to 18 carbon atoms, also known as a C₈-C₁₈ alkyl, include 1-octyl, 2-octyl, 3-octyl, 4-octyl, 6-methyl-1-heptyl, 5,5-dimethylhexyl, 1-nonyl, 2-nonyl, 1-decyl, 2-decyl, 1-tridecyl, 1-tetradecyl, 1-pentadecyl, 1-hexadecyl, 1-heptadecyl, and 1-octadecyl.

Illustrative examples of a straight or branched alkyl group or radical having from 1 to 20 carbon atoms, also known as a C₁-C₂₀ alkyl, include groups defined for C₁ to C₁₈ alkyl and 1-nonadecyl and 1-decadecyl.

An adamantyl group or radical includes 1-adamantyl and 2-adamantyl.

Illustrative examples of an alkenyl group or radical having from 2 to 6 carbon atoms, also known as a C₂ to C₆ alkenyl, include ethenyl, 1-propenyl, 2-propenyl, 1-buten-1-yl, 2-buten-1-yl, 1-penten-1-yl, 2-penten-1-yl, 1-penten-3-yl, 1-penten-5-yl, 1-hexen-1-yl, 1-hexen-4-yl, 2-hexen-1-yl, and 3-hexen-1-yl.

Illustrative examples of a straight or branched hydrocarbon chain having from 1 to 18 carbon atoms and having from 1 or 2 nonadjacent double bonds

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include ethenyl, 2-propenyl, 2-butenyl, 3-pentenyl, 2-octenyl, 5-nonenyl, 4-undecenyl, 5-heptadecenyl, 3-octadecenyl, 9-octadecenyl, 2,2-dimethyl-11-eicosenyl, and 9,12-octadecadienyl,

5 Illustrative examples of a straight or branched hydrocarbon chain having from 1 to 20 carbon atoms and having from 1 to 3 double bonds include ethenyl, 2-propenyl, 2-butenyl, 3-pentenyl, 2-octenyl, 5-nonenyl, 4-undecenyl, 5-heptadecenyl, 3-octadecenyl, 9-octadecenyl, 2,2-dimethyl-11-eicosenyl, 9,12-octadecadienyl, and 1,4,10-hexadecatrienyl.

10 Illustrative examples of a cycloalkyl group or radical having from 3 to 8 carbon atoms, also known as a C₃-C₈ cycloalkyl, include cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, and cyclooctyl.

Illustrative examples of a cycloalkyl group or radical having from 3 to 10 carbon atoms, also known as a C₃-C₁₀ cycloalkyl, include groups defined for C₃ to C₈ cycloalkyl and cyclononyl and cyclodecyl.

15 Illustrative examples of a spirocycloalkyl group or radical, which is a bicyclic group consisting of two rings sharing one and only one atom, having from 5 to 11 carbon atoms, also known as a C₅-C₁₁ spirocycloalkyl, include bicyclo[2.2.1]pentanyl, bicyclo[3.2.1]hexanyl, bicyclo[3.3.1]heptanyl, and bicyclo[5.5.1]undecanyl.

20 Illustrative examples of an aryl group or radical include phenyl, 1-naphthyl, and 2-naphthyl.

25 Illustrative examples of an alkylene group or diradical, which is a divalent radical, having from 1 to 4 carbon atoms, also known as a C₁-C₄ alkylene group or diradical, include -CH₂-, -CH₂CH₂-, -CH₂CH₂CH₂-, -CH₂CH₂CH₂CH₂-, and -CH(CH₃)CH₂CH₂-.

30 Illustrative examples of an arylalkyl group or radical, which is an aryl group or radical bonded to an C₁-C₄ alkylene group or diradical, wherein aryl and C₁ to C₄ alkylene have the meanings as defined above, include benzyl, 2-phenylethyl, 3-phenylpropyl, 4-phenylbutyl, 3-methyl-3-phenylpropyl, 1-naphthylmethyl, 1-naphthylethyl, 3-(1-naphthyl)-propyl, 4-(1-naphthyl)-butyl, and 4-(2-naphthyl)-butyl.

Illustrative examples of a phenylalkyl group or radical, which is a phenyl group or radical bonded to a C₁ to C₄ alkylene group or diradical, wherein C₁ to C₄ alkylene has the meaning as defined above, include benzyl, 2-phenylethyl, 3-phenylpropyl, 4-phenylbutyl, and 3-methyl-3-phenylpropyl.

5 An alkylidene group or diradical is a divalent radical formed by removal of one hydrogen atom from the same carbon atom of an alkyl group or radical.

A benzylidene group or diradical is a divalent radical formed by removal of one hydrogen atom from the methylene of a benzyl radical to produce "PhCH="

10 Illustrative examples of a straight or branched alkoxy group or radical having from 1 to 3 carbon atoms, also known as a C₁-C₃ alkoxy, include methoxy, ethoxy, 1-propoxy, and 2-propoxy.

 Illustrative examples of a straight or branched alkoxy group or radical having from 1 to 4 carbon atoms, also known as a C₁-C₄ alkoxy, include groups defined for C₁ to C₃ alkoxy and 1-butoxy, 2-butoxy, 2-methyl-1-propoxy, and
15 1,1-dimethylethoxy.

 Illustrative examples of a straight or branched alkoxy group or radical having from 1 to 6 carbon atoms, also known as a C₁-C₆ alkoxy, include groups defined for C₁ to C₄ alkoxy and 1-pentoxy, 2-pentoxy, 3-pentoxy, 2,2-dimethylpropoxy, 1-hexoxy, 2-hexoxy, 3-hexoxy, and 4-methyl-1-pentoxy.

20 Phenoxy means a phenyl-O- group or radical.

 Illustrative examples of a straight or branched acyloxy group or radical having from 2 to 6 carbon atoms, also known as a C₂-C₆ acyloxy, include acetyloxy, propanoyloxy, butanoyloxy, pentanoyloxy, hexanoyloxy, and 4-methylpentanoyloxy.

25 Illustrative examples of a straight or branched alkylthio group or radical having from 1 to 3 carbon atoms, also known as a C₁-C₃ alkylthio and which is a C₁-C₃ alkyl-S- group or radical, include methylthio, ethylthio, 1-propylthio, and 2-propylthio.

 Illustrative examples of a straight or branched alkylthio group or radical
30 having from 1 to 4 carbon atoms, also known as a C₁-C₄ alkylthio and which is a

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C₁-C₄ alkyl-S- group or radical, include groups defined for C₁-C₃ alkylthio and 1-butylthio and 2-butylthio.

Illustrative examples of a straight or branched alkylthio group or radical having from 1 to 20 carbon atoms, also known as a C₁-C₂₀ alkylthio and which is
5 a C₁-C₂₀ alkyl-S- group or radical, include groups defined for C₁-C₄ alkylthio and 1-pentylthio, 2-pentylthio, 3-pentylthio, 2,2-dimethylpropylthio, 1-hexylthio, 2-hexylthio, 3-hexylthio, 4-methyl-1-pentylthio, 1-heptylthio, 2-heptylthio, 3-heptylthio, 4-heptylthio, 1-octylthio, 2-octylthio, 3-octylthio, 4-octylthio, 6-methyl-1-heptylthio, 5,5-dimethylhexylthio, 1-nonylthio, 2-nonylthio, 1-decylthio,
10 2-decylthio, 1-tridecylthio, 1-tetradecylthio, 1-pentadecylthio, 1-hexadecylthio, 1-heptadecylthio, 1-octadecylthio, 1-nonadecylthio, and 1-decadecylthio.

Illustrative examples of a cycloalkylthio group or radical having from 3 to 10 carbon atoms, also known as a C₃-C₁₀ cycloalkylthio, include
cyclopropylthio, cyclobutylthio, cyclopentylthio, cyclohexylthio, cycloheptylthio,
15 cyclooctylthio, cyclononylthio, and cyclodecylthio.

Illustrative examples of a cycloalkylthio group or radical having from 5 to 7 carbon atoms, also known as a C₅-C₇ cycloalkylthio, include cyclopentylthio, cyclohexylthio, and cycloheptylthio.

Illustrative examples of an phenylalkylthio group or radical, which is a
20 phenyl group or radical bonded to a C₁-C₄ alkylene-S- group or diradical, wherein C₁ to C₄ alkylene has the meaning as defined above, include benzylthio, 2-phenylethylthio, 3-phenylpropylthio, 4-phenylbutylthio, and 3-methyl-3-phenylpropylthio.

Phenylthio means a phenyl-S- group or radical.

25 A heteroatom is nitrogen, oxygen, or sulfur.

A fused bicyclic group or radical is a group wherein two ring systems share two and only two atoms.

A fused tricyclic group or radical is a group wherein three ring systems share four and only four atoms.

30 A heteroaryl group or radical is a 5- or 6-membered, monocyclic aromatic ring group containing from 1 to 4 heteroatoms selected from nitrogen, oxygen, and sulfur, an 8- to 12-membered fused bicyclic ring group wherein at least one

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ring is aromatic and contains from 1 to 6 heteroatoms selected from nitrogen, oxygen, and sulfur, or a 12- to 14-membered fused tricyclic ring group wherein at least one ring is aromatic and contains from 1 to 6 heteroatoms selected from nitrogen, oxygen, and sulfur. Illustrative examples of monocyclic heteroaryl

5 include 2- or 3-thienyl, 2- or 3-furanyl, 1-, 2- or 3-pyrrolyl, 1-, 2- or 4-imidazolyl, 1-, 3- or 4-pyrazolyl, 2-, 4- or 5-oxazolyl, 2-, 4- or 5-thiazolyl, 3-, 4- or 5-isoxazolyl, 3-, 4- or 5-isothiazolyl, 1-, 3- or 5-(1,2,4-triazolyl), 1-, 2- or 5-(1,3,4-triazolyl), 1-, 4- or 5-(1,2,3-triazolyl), 1-, 2- or 5-tetrazolyl, 2-, 3- or 4-pyridinyl, 3- or 4-pyridazinyl, 2- or 3-pyrazinyl, and 2-, 4- or 5-pyrimidinyl. Illustrative

10 examples of bicyclic heteroaryl include 2-, 3-, 4-, 5-, 6-, 7- or 8-quinolinyl, 1-, 3-, 4-, 5-, 6-, 7- or 8-isoquinolinyl, 1-, 2-, 3-, 4-, 5-, 6- or 7-indolyl, 2-, 3-, 4-, 5-, 6- or 7-benzo[b]thienyl, 2-, 4-, 5-, 6- or 7-benzofuran, 2-, 4-, 5-, 6- or 7-benzoxazolyl, 2-, 4-, 5-, 6- or 7-benzothiazolyl, 4-, 5-, 6- or 7-benzotriazolyl, 1-, 2-, 3-, 4-, 5-, 6- or 7-benzimidazolyl, and 4-, 5-, 6- or 7-(2,1,3-benzothiadiazolyl). Illustrative

15 examples of tricyclic heteroaryl include 1-, 2-, 3- or 4-dibenzofuranyl, 1-, 2-, 3- or 4-dibenzothienyl and 1-, 2-, 3-, 4-, 5-, 6-, 7-, 8-, or 9-(1,2,3,4-tetrahydroacridinyl). All with the proviso that when bonded to a heteroatom, the heteroaryl group or radical is connected via a carbon atom.

A heterocycloalkyl group or radical is a 3-, 4-, 5-, 6- or 7-membered,

20 monocyclic nonaromatic ring group containing from 1 to 3 heteroatoms selected from nitrogen, oxygen, or sulfur, a 9- to 12-membered fused bicyclic ring group wherein at least one ring is nonaromatic and contains from 1 to 4 heteroatoms selected from nitrogen, oxygen, or sulfur, or a 12- to 15-membered fused tricyclic ring group wherein at least one ring is nonaromatic and contains from 1 to

25 4 heteroatoms selected from nitrogen, oxygen, or sulfur. Illustrative examples of monocyclic heterocycloalkyl include 2- or 3-tetrahydrofuranyl, 1-, 2- or 3-pyrrolidinyl, 1-, 2-, 3- or 4-piperidinyl, 2-, 3- or 4-morpholinyl, 2-, 3- or 4-thiomorpholinyl, 2-, 3-, or 4-tetrahydropyranyl, 2-dioxanyl, 1-, 2-, 3- or 4-azacycloheptanyl, 1- or 2-aziridinyl, or 1- or 2-piperazinyl. Illustrative examples

30 of bicyclic heterocycloalkyl include 1-, 2-, 3-, 4-, 5-, 6-, 7- or 8-(1,2,3,4-tetrahydroquinolinyl), 1-, 2-, 3-, 4-, 5-, 6-, 7- or 8-(1,2,3,4-tetrahydroisoquinolinyl), 1-, 2-, 3-, 4-, 5-, 6- or 7-indolinyl, 1-, 2-, 3-, 4-, 5-, 6- or 7-isindolinyl, and 2-, 3-, 4-, 5-, 6- or 7-(2,3-dihydrobenzofuranyl). Illustrative

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examples of tricyclic heterocycloalkyl include 1-, 2-, 3-, 4-, 5-, 6-, 7- or 8-(9,10-dihydroacridinyl) and 1-, 2-, 3-, 4-, 5-, 6-, 7-, 8- or 9-xanthenyl. All with the proviso that when bonded to a heteroatom, the heterocycloalkyl group or radical is connected via a carbon atom.

5 A heteroaryloxy group or radical is a heteroaryl-O- group wherein heteroaryl has the meaning as defined above.

 A heteroarylthio group or radical is a heteroaryl-S- group wherein heteroaryl has the meaning as defined above.

 Halogen means bromine, chlorine, fluorine, or iodine.

10 Pharmaceutically acceptable salts of the compounds of Formula I and II are also included as a part of the present invention.

 The base salts may be generated from compounds of Formula I or II by reaction of the latter with one equivalent of a suitable nontoxic, pharmaceutically acceptable base followed by evaporation of the solvent employed for the reaction and recrystallization of the salt, if required. The compounds of Formula I or II
15 may be recovered from the base salt by reaction of the salt with an aqueous solution of a suitable acid such as hydrobromic, hydrochloric, or acetic acid.

 Suitable bases for forming base salts of the compounds of this invention include amines such as triethylamine or dibutylamine, or alkali metal bases and
20 alkaline earth metal bases. Preferred alkali metal hydroxides and alkaline earth metal hydroxides as salt formers are the hydroxides of lithium, sodium, potassium, magnesium, or calcium. The class of bases suitable for the formation of nontoxic, pharmaceutically acceptable salts is well-known to practitioners of the pharmaceutical formulation arts. See, for example, Berge S.N., et al, J. Pharm. Sci., 1977;66:1-19.
25

 Suitable acids for forming acid salts of the compounds of this invention containing a basic group include, but are not necessarily limited to acetic, benzoic, benzenesulfonic, tartaric, hydrobromic, hydrochloric, citric, fumaric, gluconic, glucuronic, glutamic, lactic, malic, maleic, methanesulfonic, pamoic, salicylic,
30 stearic, succinic, sulfuric, and tartaric acids. The acid addition salts are formed by procedures well-known in the art.

 The compounds of the present invention may also exist in different stereoisomeric forms by virtue of the presence of asymmetric centers in the

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compound. The present invention contemplates all stereoisomeric forms of the compounds as well as mixtures thereof, including racemic mixtures.

Further, the compounds of this invention may exist in unsolvated as well as solvated forms with pharmaceutically acceptable solvents such as water,
5 ethanol and the like. In general, the solvated forms are considered equivalent to the unsolvated forms for the purposes of this invention.

ACAT inhibitors of Formula I useful in the practice of this invention may be selected from:

Sulfamic acid (phenylacetyl)-2,6-bis(1-methylethyl)phenyl ester,

10 Sulfamic acid [[2,6-bis(1-methylethyl)phenyl]acetyl]-2,6-bis(1-methylethyl)phenyl ester,

Sulfamic acid [[2,4,6-tris(1-methylethyl)phenyl]acetyl]-
2,4,6-tris(1-methylethyl)phenyl ester,

Sulfamic acid [[2,6-bis(1-methylethyl)phenyl]acetyl]-2,4,6-tris(1-methyl-
15 ethyl)-phenyl ester,

Sulfamic acid [adamantaneacetyl]-2,6-bis(1-methylethyl)phenyl ester,

Sulfamic acid [[2,6-bis(1-methylethyl)phenyl]acetyl]-2,6-bis(1-methylethyl)phenyl ester-sodium salt,

Sulfamic acid [[2,4,6-tris(1-methylethyl)phenyl]acetyl]-2,6-bis(1-methylethyl)phenyl ester-sodium salt,
20

Sulfamic acid (decanoyl)-2,6-bis-(1-methylethyl)phenyl ester,

Sulfamic acid (dodecanoyl)-2,6-bis-(1-methylethyl)phenyl ester,

2,6-Bis(1-methylethyl)-N-[[[2,4,6-tris(1-methylethyl)phenyl]methyl]-sulfonyl]benzeneacetamide,

25 2,6-Bis(1-methylethyl)-N-[[[2,4,6-tris(1-methylethyl)phenyl]methyl]-sulfonyl]benzeneacetamide-sodium salt,

2,6-Bis(1-methylethyl)phenyl[[[2,4,6-tris(1-methylethyl)phenyl]methyl]-sulfonyl]carbamate,

2,6-Bis(1-methylethyl)phenyl[[[2,4,6-tris(1-methylethyl)phenyl]methyl]-sulfonyl]carbamate-sodium salt,
30

Sulfamic acid (1-oxo-3,3-diphenylpropyl)-2,6-bis(1-methylethyl)phenyl ester,

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- Sulfamic acid [2,6-dichlorophenyl(acetyl)]-2,6-bis(1-methylethyl)phenyl ester,
- Sulfamic acid [2,6-dichlorophenyl(acetyl)]-2,6-bis(1-methylethyl)phenyl ester,
- 5 Sulfamic acid trans-[(2-phenylcyclopropyl)carbonyl]-2,6-bis(1-methylethyl)phenyl ester,
- Sulfamic acid [2,5-dimethoxyphenyl(acetyl)]-2,6-bis(1-methylethyl)phenyl ester,
- Sulfamic acid [2,4,6-trimethoxyphenyl(acetyl)]-2,6-bis(1-methylethyl)phenyl ester,
- 10 Sulfamic acid [2,4,6-trimethylphenyl(acetyl)]-2,6-bis(1-methylethyl)phenyl ester,
- Sulfamic acid [2-thiophenyl(acetyl)]-2,6-bis(1-methylethyl)phenyl ester,
- Sulfamic acid [3-thiophenyl(acetyl)]-2,6-bis(1-methylethyl)phenyl ester,
- 15 Sulfamic acid [2-methoxyphenyl(acetyl)]-2,6-bis(1-methylethyl)phenyl ester,
- Sulfamic acid (oxophenylacetyl)-2,6-bis(1-methylethyl)phenyl ester,
- Sulfamic acid [2-trifluoromethylphenyl(acetyl)]-2,6-bis(1-methylethyl)phenyl ester,
- 20 Sulfamic acid (1-oxo-2-phenylpropyl)-2,6-bis(1-methylethyl)phenyl ester,
- Sulfamic acid (cyclopentylphenylacetyl)-2,6-bis(1-methylethyl)phenyl ester,
- Sulfamic acid (cyclohexylacetyl)-2,6-bis(1-methylethyl)phenyl ester,
- Sulfamic acid (diphenylacetyl)-2,6-bis(1-methylethyl)phenyl ester,
- 25 Sulfamic acid (triphenylacetyl)-2,6-bis(1-methylethyl)phenyl ester,
- Sulfamic acid [(1-phenylcyclopentyl)carbonyl]-2,6-bis(1-methylethyl)phenyl ester,
- Sulfamic acid (3-methyl-1-oxo-2-phenylpentyl)-2,6-bis(1-methylethyl)phenyl ester,
- 30 Sulfamic acid (1-oxo-2-phenylbutyl)-2,6-bis(1-methylethyl)phenyl ester,
- Sulfamic acid (cyclohexylphenylacetyl)-2,6-bis(1-methylethyl)phenyl ester,

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Sulfamic acid (1-oxo-2,2-diphenylpropyl)-2,6-bis(1-methylethyl)phenyl ester,

Sulfamic acid [(9H-fluoren-9-yl)carbonyl]-2,6-bis(1-methylethyl)phenyl ester,

5 Sulfamic acid (1-oxo-3-phenylpropyl)-2,6-bis(1-methylethyl)phenyl ester,

Sulfamic acid [1-oxo-3-[2,4,6-tris(1-methylethyl)phenyl]-2-propenyl]-2,6-bis(1-methylethyl)phenyl ester,

Sulfamic acid [1-oxo-3-[2,4,6-tris(1-methylethyl)phenyl]propyl]-2,6-bis(1-methylethyl)phenyl ester,

10 Sulfamic acid [(acetyloxy)[2,4,6-tris(1-methylethyl)phenyl]acetyl]-2,6-bis(1-methylethyl)phenyl ester,

Sulfamic acid [hydroxy[2,4,6-tris(1-methylethyl)phenyl]acetyl]-2,6-bis(1-methylethyl)phenyl ester,

15 Sulfamic acid [fluoro[2,4,6-tris(1-methylethyl)phenyl]acetyl]-2,6-bis(1-methylethyl)phenyl ester,

Sulfamic acid (3-methyl-1-oxo-2-phenylpentyl)-2,6-bis(1-methylethyl)phenyl ester sodium salt,

Sulfamic acid [[2,4,6-tris(1-methylethyl)phenoxy]acetyl]-2,6-bis(1-methylethyl)phenyl ester,

20 Sulfamic acid [[2,6-bis(1-methylethyl)phenoxy]acetyl]-2,6-bis(1-methylethyl)phenyl ester, and

Sulfamic acid [[2,4,6-tris(1-methylethyl)phenyl]acetyl]-2,6-bis(phenyl)-phenyl ester.

25 ACAT inhibitors of Formula II useful in the practice of this invention may be selected from:

N-[2,6-Bis(1-methylethyl)phenyl]-2-dodecyl-2H-tetrazole-5-acetamide;

2-Dodecyl-N-(2,4,6-trimethoxyphenyl)-2H-tetrazole-5-acetamide;

N-(2,4-Difluorophenyl)-2-dodecyl-2H-tetrazole-5-acetamide;

2-Tetradecyl-N-(2,4,6-tri-methoxyphenyl)-2H-tetrazole-5-acetamide;

30 N-(4,6-Dimethoxy-5-pyrimidinyl)-2-dodecyl-2H-tetrazole-5-acetamide;

N-(4,6-Dimethoxy-5-pyrimidinyl)-2-dodecyl-1H-tetrazole-5-acetamide;

2-Dodecyl-N-(3-methyl-2-pyridinyl)-2H-tetrazole-5-acetamide;

2-Dodecyl-N-(1,3,5-trimethyl-1H-pyrazol-4-yl)-2H-tetrazole-5-acetamide;

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- 1-Dodecyl-N-(1,3,5-trimethyl-1H-pyrazol-4-yl)-1H-tetrazole-5-acetamide;
(±) 2-Dodecyl- α -phenyl-N-(2,4,6-trimethoxyphenyl)-2H-tetrazole-
5-acetamide;
(±) 2-Dodecyl-N, α -diphenyl-2H-tetrazole-5-acetamide;
5 (±)-N-[2,6-bis(1-Methylethyl)phenyl]-2-dodecyl- α -phenyl-2H-tetrazole-
5-acetamide;
(±)-N-(2,4-Difluorophenyl)-2-dodecyl- α -phenyl-2H-tetrazole-
5-acetamide;
(±)-2-Octyl- α -phenyl-N-(2,4,6-trimethoxyphenyl)-2H-tetrazole-
10 5-acetamide;
(±)-2-Hexadecyl- α -phenyl-N-(2,4,6-trimethoxyphenyl)-2H-tetrazole-
5-acetamide;
(±)-N-(4,6-Dimethoxy-5-pyrimidinyl)-2-dodecyl- α -phenyl-2H-tetrazole-
5-acetamide;
15 (±)-N-(5,7-Dimethyl-1,8-naphthyridine-2-yl)-2-dodecyl- α -phenyl-2H-
tetrazole-5-acetamide;
(±)-2-Dodecyl- α -phenyl-N-(1,3,5-trimethyl-1H-pyrazol-4-yl)-2H-
tetrazole-5-acetamide;
(±)-N-Cyclopropyl-2-dodecyl- α -phenyl-2H-tetrazole-5-acetamide;
20 (±)-2-Dodecyl- α -phenyl-N-2-pyridinyl-2H-tetrazole-5-acetamide;
(±)-2-Dodecyl-N-(3-methyl-2-pyridinyl)- α -phenyl-2H-tetrazole-
5-acetamide;
(±)-2-Dodecyl-N-(3-methyl-2-pyridinyl)-2-phenyl-2H-tetrazole-
5-acetamide, N-oxide;
25 (±)-N-(1,1-Dimethylethyl)-2-dodecyl- α -phenyl-2H-tetrazole-5-acetamide;
(±)-2-Dodecyl- α -(2-pyridyl)-N-(2,4,6-trimethoxyphenyl)-2H-tetrazole-
5-acetamide;
(±)-N-[2,6-Bis(1-methylethyl)phenyl]-2-dodecyl- α -2-pyridinyl-2H-
tetrazole-5-acetamide;
30 2-Dodecyl- α , α -dimethyl-N-(2,4,6-trimethoxyphenyl)-2H-tetrazole-
5-acetamide;

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2-Dodecyl- α,α' -(2-propenyl)-N-(2,4,6-trimethoxyphenyl)-2H-tetrazole-5-acetamide;

1-(2-Dodecyl-2H-tetrazol-5-yl)-N-(2,4,6-trimethoxyphenyl)-cyclopentanecarboxamide;

5 2-Tridecyl- α,α -dimethyl-N-(2,4,6-trimethoxyphenyl)-2H-tetrazole-5-acetamide;

2-Dodecyl-N-(2,4,6-trimethoxyphenyl)-2H-tetrazole-5-propanamide;

N-(2,6-bis(1-Methylethyl)phenyl)-2-dodecyl-2H-tetrazole-5-propanamide;

N-(2,4-Difluorophenyl)-2-dodecyl-2H-tetrazole-5-propanamide;

10 1-Dodecyl-N-(2,4,6-trimethoxyphenyl)-1H-tetrazole-5-propanamide;

(\pm)-n-(2,4-Difluorophenyl)-1-dodecyl- α -phenyl-1H-tetrazole-5-acetamide;

(\pm)-N-[2,6-bis(1-Methylethyl)phenyl]-1-dodecyl- α -phenyl-1H-tetrazole-

5-acetamide;

(\pm)-2-Dodecyl- α -methyl- α -phenyl-N-(2,4,6-trimethoxyphenyl)-2H-

15 tetrazole-5-acetamide;

(\pm)-2-Dodecyl- α -(4-fluorophenyl)-N-(2,4,6-trimethoxyphenyl)-2H-

tetrazole-5-acetamide;

(\pm)-2-Dodecyl- α -2-naphthalenyl-N-(2,4,6-trimethoxyphenyl)-2H-

tetrazole-5-acetamide;

20 (\pm)- α -([1,1'-Biphenyl]-4-yl)-2-dodecyl-N-(2,4,6-trimethoxy-phenyl)-2H-

tetrazole-5-acetamide;

(\pm)-2-Dodecyl- α -methyl-N-(2,4,6-trimethoxy-phenyl)-2H-tetrazole-

5-acetamide;

(\pm)-2-Dodecyl- α -phenylmethyl-N-(2,4,6-trimethoxyphenyl)-2H-tetrazole-

25 5-acetamide;

(\pm)-2-Dodecyl- α -cyclohexyl-N-(2,4,6-trimethoxy-phenyl)-2H-tetrazole-

5-acetamide;

(-)-2-Dodecyl- α -phenyl-N-(2,4,6-trimethoxy-phenyl)-2H-tetrazole-

5-acetamide [α]_D = -58° (1% in CH₃OH);

30 (+)-2-Dodecyl- α -phenyl-N-(2,4,6-trimethoxy-phenyl)-2H-tetrazole-

5-acetamide [α]_D = +55.1° (1% in CH₃OH);

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(±)-N-[2,6-Bis(1-Methylethyl)phenyl]-2-dodecyl- α -fluoro- α -phenyl-2H-tetrazole-5-acetamide;

(±)-2-Dodecyl- α -fluoro- α -phenyl-N-(2,4,6-trimethoxy phenyl)-2H-tetrazole-5-acetamide;

5 N-[2,6-bis(1-Methylethyl)phenyl]-5-decyl-2H-tetrazole-2-acetamide;
N-[2,6-bis(1-Methylethyl)phenyl]-5-dodecyl-2H-tetrazole-2-acetamide;
(±)-N-[2,6-bis(1-Methylethyl)phenyl]-5-dodecyl- α -phenyl-2H-tetrazole-2-acetamide;

10 (±)-N-[2,6-bis(1-Methylethyl)phenyl]-5-dodecyl- α -pentyl-2H-tetrazole-2-acetamide;

(±)-N-[2,6-bis(1-Methylethyl)phenyl]-5-(dodecylthio)- α -phenyl-2H-tetrazole-2-acetamide;

(±)-5-Decyl- α -phenyl-N-(2,4,6-trimethoxyphenyl)-2H-tetrazole-2-acetamide;

15 5-Dodecyl-N-(2,4,6-trimethoxy-phenyl)-2H-tetrazole-2-acetamide;
(±)-5-Dodecyl- α -phenyl-N-(2,4,6-trimethoxyphenyl)-2H-tetrazole-2-acetamide;

(±)-5-Dodecyl- α -pentyl-N-(2,4,6-trimethoxyphenyl)-2H-tetrazole-2-acetamide;

20 (±)-N-(2,4-Difluorophenyl)-5-dodecyl- α -phenyl-2H-tetrazole-2-acetamide;

5-Dodecyl- α , α -dimethyl-N-(2,4,6-trimethoxyphenyl)-2H-tetrazole-2-acetamide;

25 (±)-5-(Dodecylthio)- α -phenyl-N-(2,4,6-trimethoxyphenyl)-2H-tetrazole-2-acetamide; or

(±)-5-(Dodecylsulfinyl)- α -phenyl-N-(2,4,6)-trimethoxyphenyl)-2H-tetrazole-2-acetamide.

Still further, other ACAT inhibitors useful in the practice of this invention may be selected from:

30 4-Hexadecylamino-benzoic acid monosodium salt;

3,5-Dimethyl-1-[5-(1,4,5-triphenyl-2H-imidazol-2-yl)sulfanyl]-pentyl]-1H-pyrazole monosodium salt;

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- 8-(1,4,5-Triphenyl-2H-imidazol-2-yloxy)-octanoic acid;
 9-Bromo-6,11-dihydro-dibenzo[b,e]oxepine-11-carboxylic acid
 (2,6-diisopropyl-phenyl)-amide;
 5-((3,5-Di-tert-butyl-4-hydroxy-phenylamino)-{[4-(2,2-dimethyl-propyl)-
 5 benzyl]-hexyl-amino}-methylene)-2,2-dimethyl-[1,3]dioxane-4,6-dione;
 3-(2,4-Difluoro-phenyl)-1-[4-(2,2-dimethyl-propyl)-benzyl]-1-heptyl-urea;
 1-Heptyl-1-[4-(3-methyl-butyl)-benzyl]-3-(2,4,6-trifluoro-phenyl)-urea;
 3-(2,4-Difluoro-phenyl)-1-[5-(4,5-diphenyl-1H-imidazol-2-ylsulfanyl)-
 pentyl]-1-heptyl-urea;
 10 1-Butyl-3-{2-[3-(5-ethyl-4-phenyl-imidazol-1-yl)-propoxy]-6-methyl-
 phenyl}-urea;
 1-(2-{2-[4-(2,2-Dimethyl-propyl)-phenyl]-ethyl}-4,6-difluoro-phenyl)-
 3-heptyl-urea;
 Octadeca-9,12-dienoic acid (1-phenyl-ethyl)-amide;
 15 3-(1H-Indol-3-yl)-2-octadec-9-enoylamino-propionic acid ethyl ester;
 3-(Dimethyl-nonyl-silanyl)-N-(1-phenyl-2-p-tolyl-ethyl)-propionamide;
 (R)2-Hexyl-decanoic acid (6-methyl-2,4-bis-methylsulfanyl-pyridin-3-yl)-
 amide;
 N-[2-(3,5-Di-tert-butyl-4-hydroxy-phenyl)-ethyl]-4-fluoro-
 20 benzenesulfonamide;
 2-(2-Ethoxy-ethylsulfanyl)-4,5-diphenyl-1H-imidazole;
 4-Cyano-N-[2-(4-cyano-phenyl)-3-methyl-5,5-bis-trifluoromethyl-
 4,5-dihydro-3H-imidazol-4-yl]-N-methyl-benzamide;
 1-{3-[3-(1-Methyl-1H-imidazol-2-yl)-2-phenethyl-2H-chromen-6-yloxy]-
 25 propyl}-cyclopentanecarboxylic acid ethyl ester;
 1-[4-(2-Chloro-phenyl)-2-ethyl-thieno[2,3-b]pyridin-5-yl]-3-(2,4-difluoro-
 phenyl)-urea;
 1-(2-Cyclohexyl-[1,3]dithiolan-2-ylmethyl)-3-(2,6-diisopropyl-phenyl)-
 urea;
 30 1-Cycloheptyl-1-(2,3-dihydro-benzo[1,4]dioxin-5-ylmethyl)-
 3-(2,4,6-trimethyl-phenyl)-urea;
 1-{2-[4-(1,2-Dimethoxy-ethoxy)-phenyl]-ethyl}-3-(2,4-dimethoxy-
 phenyl)-1-heptyl-urea;

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2-(4-{2-[3-(2,4-Dimethoxy-phenyl)-1-heptyl-ureido]-ethyl}-phenoxy)-
2-methyl-propionic acid;

3-(2,4-Difluoro-phenyl)-1-octyl-1-(2,3,4,5-tetrahydro-benzo[b]oxepin-
5-yl)-urea;

5 N-(2,6-Diisopropyl-phenyl)-2-octadecylsulfanyl-acetamide;

2-Bromo-6,11-dihydro-dibenzo[b,e]oxepine-11-carboxylic acid
(2,6-diisopropyl-phenyl)-amide;

(±)N-(1,2-Diphenyl-ethyl)-3-(2-heptyloxy-phenyl)-propionamide;

2,2-Dimethyl-dodecanoic acid (7-methoxy-4-oxo-chroman-8-yl)-amide;

10 (Z)1-(6,7-Dimethoxy-3,4-dihydro-1H-isoquinolin-2-yl)-octadec-9-en-1-1;

(Z)2,2,5,5-Tetramethyl-[1,3]dioxane-4-carboxylic acid [2-(2-octadec-
9-enoylamino-ethylcarbamoyl)-ethyl]-amide;

1-Benzyl-1-(5-methyl-3-phenyl-benzofuran-2-ylmethyl)-3-(2,4,6-trifluoro-
phenyl)-urea;

15 5-Chloro-3-o-tolyl-benzofuran-2-carboxylic acid (2,6-diisopropyl-phenyl)-
amide;

2-(2,4a-Dimethyl-4a,5-dihydro-naphthalen-1-ylsulfanyl)-N-
{2-[(6,6-dimethyl-hepta-2,4-diynyl)-pentyl-amino]-ethyl}-acetamide;

20 (Z)Octadec-9-enoic acid [2-(1,4-dioxo-8-aza-spiro[4.5]dec-8-yl)-1-phenyl-
ethyl]-amide;

N-(4-Dihexylamino-6-mercapto-2-methyl-pyrimidin-5-yl)-4-(phenyl-
propyl-amino)-butyramide;

(Z)1-(6,7-Dimethoxy-3-phenyl-3,4-dihydro-1H-isoquinolin-2-yl)-octadec-
9-en-1-1;

25 (trans)1,4-Bis-(4-methoxy-phenyl)-3-(3-phenyl-propyl)-azetidin-2-1;

1-Butyl-3-{2-dimethylamino-6-[3-(4-phenyl-imidazol-1-yl)-propoxy]-
phenyl}-urea;

1-{2-Dimethylamino-6-[3-(4-phenyl-imidazol-1-yl)-propoxy]-phenyl}-
3-pentyl-urea;

30 1-{2-Dimethylamino-6-[3-(5-methyl-4-phenyl-imidazol-1-yl)-propoxy]-
phenyl}-3-pentyl-urea;

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1-(2-{2-[4-(2,2-Dimethyl-propyl)-phenyl]-ethyl}-4,6-difluoro-phenyl)-
3-heptyl-urea;

(4S-trans)6-(4,5-Diphenyl-1H-imidazol-2-ylsulfanylmethyl)-4-hydroxy-
4-methyl-tetrahydro-pyran-2-1;

5 2-(3-[1,3]Dioxan-2-yl-propylsulfanyl)-4,5-diphenyl-1H-imidazole;

Hydroxy-phenyl-acetic acid 3,3,5-trimethyl-cyclohexyl ester;

Acetic acid 1-(11-hydroxy-4-methoxy-9-methyl-5-oxo-5H,7H-6,12-dioxo-
dibenzo[a,d]-cycloocten-3-yl)-3-methyl-butyl ester;

10 10-Hydroxy-2,4a,6a,6b,9,10,12a-heptamethyl-4-octadecanoyloxy-
1,2,3,4,4a,5,6, 6a,6b,7,8,8a,9,10, 11,12,12a,12b,13,14b-eicosahydro-picene-
2-carboxylic acid;

3-[(2,2,5,5-Tetramethyl-[1,3]dioxane-4-carbonyl)-amino]-propionic acid
2-[3-(2,2-dimethyl-propyl)-3-nonyl-ureido]-cyclohexyl ester;

1-(2,6-Diisopropyl-phenyl)-3-(2-p-tolyl-heptyl)-urea;

15 1-[4-(2-Chloro-phenyl)-6,8-dimethyl-quinolin-3-yl]-3-(2,4-difluoro-
phenyl)-urea;

1-[4-(2-Chloro-phenyl)-1,6,7-trimethyl-2-oxo-1,2-dihydro-quinolin-3-yl]-
3-(2,4-difluoro-phenyl)-urea;

20 1-[4-(2-Chloro-phenyl)-6,7-dimethyl-2-oxo-2H-chromen-3-yl]-
3-(2,4-difluoro-phenyl)-urea;

(S)1-[6-Bromo-5-(2-chloro-phenyl)-1,3-dimethyl-2-oxo-2,3-dihydro-1H-
benzo[e][1,4]-diazepin-7-yl]-3-(2-hydroxy-1-hydroxymethyl-1-methyl-ethyl)-
urea;

25 3-(4,5-Diphenyl-1H-imidazol-2-ylsulfanylmethyl)-1-methyl-piperidine;

2-(5,5-Dimethyl-[1,3]dioxan-2-yl)-4,5-diphenyl-1H-imidazole;

2,2-Dimethyl-5-[3-(1-methyl-1H-imidazol-2-yl)-2-propyl-chroman-
6-yloxy]-pentanoic acid ethyl ester;

N-(4-Hexadecylamino-benzoyl)-4-methyl-benzenesulfonamide;

30 2-(4-Chloro-phenyl)-6-cyclohexyl-4-(2-oxo-2-phenyl-ethyl)-6,7-dihydro-
4H-1,4,6,8a-tetraaza-s-indacene-5,8-di1;

[2-(3-tert-Butyl-4-hydroxy-naphthalen-1-yl)-1-(diethoxy-phosphoryl)-
vinyl]-phosphonic acid dithyl ester;

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5-[1-(acetyloxy)-3-methylbutyl]-2'-(hydroxymethyl)-4-methoxy-4'-methylspiro[benzofuran-2(3H),1'-cyclohexa-2',4'-diene]-3,6'-di1;

5-[1-(acetyloxy)-3-methylbutyl]-4-methoxy-4'-methyl-3,6-dioxospiro[benzofuran-2(3H),1'-cyclohexa-2',4'-diene]-2'-carboxaldehyde;

5 (3 α ,4 α ,22 α ,24 α)-3-hydroxy-22-[(1-oxooctadecyl)oxy]-24-norolean-12-en-29-oic acid;

1-[5-(4,5-Diphenyl-1H-imidazole-2-sulfinyl)-pentyl]-3,5-dimethyl-1H-pyrazole;

10 N-butyl-3-[[[(4-decyloxyphenyl)carbonyl]-amino]-4-(methylthio)-benzamide;
N,N'-1,11-Undecanediy1bis[2,3-dihydro-2-methyl]-1*H*-indole-1-carboxamide;

N,N'-[1,3-Phenylenebis(methylene)]bis[*N*-cycloheptyl-*N'*-[4-(dimethylamino)phenyl]]-urea; and

15 1-[5-[(S)-(4,5-Diphenyl-1*H*-imidazol-2-yl)sulfinyl]pentyl]-4,5-dihydro-3,5-dimethyl-1*H*-pyrazole.

Methods for determining the ability of compounds to inhibit the enzyme ACAT are well-known in the art. For example, methods are taught in United States Patents 5,491,172; 5,633,287; and 5,441,975. These patents were previously incorporated herein by reference. Further references to such methods may be found
 20 in the teachings referenced in (i) Krause B.R. and Bocan T.M.A., in: Ruffolo R.R. and Hollinger M.A., eds. Inflammation: Mediators and Pathways, 1995;173-98 (ii) Krause B. R., Sliskovic D. R. and Bocan T.M.A., Exp. Opin. Invest. Drugs, 1995;4:353-387 (iii) Roth B.D., Drug Discovery Today, 1998;3:19-25 (iv) Bocan T.M.A., Curr. Pharm. Design, 1998;4:39-53. These articles are incorporated herein
 25 by reference. The ability of ACAT inhibitors to inhibit the accumulation of monocyte-macrophages and reduce expression of MMPs in atherosclerotic lesions is described below.

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METHODS

Experimental Design. Male New Zealand White rabbits from Kuiper Farms (Gary, IN) weighing 1.2 to 1.5 kg were meal-fed a chow diet (Purina 5321) supplemented with 0.5% cholesterol, 3% peanut oil, and 3% coconut oil diet for a total of 9 weeks followed by a 0% cholesterol, 3% peanut oil, and 3% coconut oil diet (chow/fat diet) for 6 weeks prior to a 7- to 8-week administration of the ACAT inhibitor, avasimibe, in the chow/fat diet. The dietary regimen consisted of feeding 30 g for the first week, 40 g for 2 weeks, 50 g for 2 weeks, 60 g for 4 weeks, 70 g for the next 6 weeks, and 80 g for the final 7 to 8 weeks. After 1 week of diet initiation, a chronic endothelial injury was induced in the abdominal aorta and femoral artery by surgically inserting a sterile, indwelling, 18-cm nylon monofilament with a diameter of 200 μ m into the lumen of the right femoral artery. Surgical procedures were performed on animals anesthetized with 10 mg/kg xylazine from MILES (Shawnee Mission, KS) and 33 mg/kg ketamine HCL from Fort Dodge Laboratories (Fort Dodge, IA) in accordance with a vertebrate use form approved by the Parke-Davis institutional review board. After the initial 15-week lesion induction phase, which consisted of both a hypercholesterolemia and dietary normalization phase, animals were assigned on the basis of their 24-hour post-meal plasma total cholesterol values into groups such that there were no statistical differences in plasma cholesterol levels. A total of 48 animals were used. A group of animals, termed the time zero control (n = 16), was necropsied prior to drug administration while a second group, termed the progression control (n = 16), was maintained on the chow/fat diet for the remaining 7-8 weeks of the study. An additional group (n = 16) of animals was given 25 mg/kg avasimibe as an admixture to the chow/fat diet for the next 7-8 weeks. Plasma and vascular lipid levels and histologic and morphometric measurements were made on all animals. Plasma and tissue drug levels (n = 8) as well as vascular MMP expression were assessed in a subset of animals, i.e., n = 4-6 by MMP zymography and n = 8 by Northern analysis for MMP and TIMPs. The drug diet was prepared fresh on a biweekly basis.

Biochemical Methods. Plasma total cholesterol and triglyceride levels were measured enzymatically throughout the study on an Abbott VP Series II

Bichromatic Analyzer (Chicago, IL) with the Boehringer-Mannheim total cholesterol reagent (Indianapolis, IN) and the Abbott triglyceride reagent (Chicago, IL). The lipid measurements were made monthly or biweekly throughout the study on plasma samples collected 24 hours post-meal.

5 Plasma and vascular avasimibe concentrations were obtained in a group of 8 animals receiving 25 mg/kg avasimibe for 7 to 8 weeks that were not used to make the morphologic and biochemical measurements; however, gross lesion extents were comparable in both avasimibe treatment groups. Plasma samples from avasimibe-treated animals were obtained after 7 weeks of dosing at 0, 1, 2, 4,
10 8, and 24 hours post-dose, and plasma concentrations were determined using a liquid chromatographic mass spectrometric assay. Avasimibe and the internal standard, [$^{13}\text{C}_6$]avasimibe, were extracted from plasma using diethyl ether. The ether layer was evaporated to dryness and the residue reconstituted in acetonitrile:water (70:30). The chromatography conditions consisted of using
15 $2.1 \times 150 \text{ mm} \times 5 \mu\text{m}$ Zorbax RX-C18 column with a mobile phase of acetonitrile:5 mM ammonium acetate buffer (70:30) at a flow rate of 0.2 mL/min. Analytes were detected by mass spectrometry. Vascular avasimibe levels were quantified in a similar manner to that noted above for plasma; however, 100 to 200 mg of aortic arch tissue was homogenized in 2 to 4 mL of water prior to
20 extraction with diethyl ether. Aortic arch samples were collected 24 hours post-dose after 8 weeks of 25 mg/kg avasimibe.

A 3-cm segment of the iliac-femoral artery adjacent to that collected for histologic evaluation and the descending thoracic aorta were assayed for their total cholesterol, CE, free cholesterol, and total phospholipid content as previously
25 described. The lipids were extracted in chloroform:methanol (2:1) by the procedure of Folch I., Lees M., Sloane-Stanley G.H., J. Biol. Chem., 1957;226:497-509. The lipid composition of the iliac-femoral artery and descending thoracic aorta was measured with an Iatroscan TH-10 Mark IV TLC-FID analyzer from RSS Inc. (thin-layer chromatography-flame ionization
30 detection; Jackson, TN) attached to a Hewlett-Packard 3390A integrator (Palo Alto, CA).

Macrophage Cell Culture Methods. The IC_{50} of avasimibe against

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macrophage ACAT was evaluated in cultured human monocyte-derived macrophages. Human monocyte-derived macrophages supplied by Advanced Biotechnology, Inc. (Columbia, MD) were elutriated from blood of normal adult donors as previously described. Frozen but viable monocytes (20×10^6 cells/vial) were thawed and plated into 6-well plates containing RPMI 1640 media, 10% FBS obtained from HyCl1 Laboratories (Logan, UT), 1 ng/mL GM-CSF from R&D Systems (Minneapolis, MN) for 10 days to promote monocyte differentiation. On Day 10, the cells were washed and incubated with RPMI 1640, 1% Hu-Nutridoma from Boehringer Mannheim (Indianapolis, IN) and 1 ng/mL GM-CSF for an additional 24 hours. The culture media was changed from RPMI 1640 with 1% pen/strep, 10% FBS and 1 ng/mL GM-CSF to RPMI 1640 with 1% pen/strep, 1% Nutridoma Hu, and 1 ng/mL GM-CSF. Avasimibe was dissolved in DMSO and was added at concentrations of 10 to 1000 nM for 1 hour prior to addition of 37 μ g/mL acetylated LDL supplied by PerImmune, Inc. (Rockville, MD). After a 24 hour incubation, the internal standard, 1,2-hexadecanediol purchased from Aldrich Chem. (Milwaukee, WI) was added at 37.5 μ g/mL to each well and lipids were extracted with 1 mL of hexane:isopropanol (3:2). After extraction, the organic phase was dried under nitrogen, redissolved in iso-octane/tetrahydrofuran (97:3) and the free cholesterol, CE and triglyceride content of the cells was quantified using an HPLC method. In separate cultures treated in a similar fashion to that noted above for determination of the IC₅₀ of avasimibe against macrophage ACAT, the media was removed and MMP activity was assessed by gelatin zymography.

Zymography Methods. Aortic matrix metalloproteinase expression was assessed in the aortic arch of 4 to 6 animals from the progression control and avasimibe treatment group. Specimens of aortic arch were stored at -70°C prior to extraction of tissue MMPs according to the procedure described by Galis et al. Tissue samples were minced and homogenized in ice-cold 10 mM sodium phosphate buffer (pH 7.2) containing 150 mM sodium chloride, 1% Triton X-100, 0.1% SDS, 0.5% sodium deoxycholate, and 0.2% sodium azide. Tissue homogenates were centrifuged at 14000 RPM for 10 minutes at 4°C and the supernatant collected. Protein content was measured using a BioRad protein assay

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and SDS-PAGE zymography was performed on the extracted tissue specimens. 1 part tissue homogenate containing 30 µg protein was mixed with 1 part 2X sodium dodecyl sulfate (SDS) sample buffer from Novex (San Diego, CA) and molecular weight markers were added. Each sample was loaded on either a 10% polyacrylamide gel containing 0.1% gelatin purchased precast from Novex (San Diego, CA) or 4-16% acrylamide gel containing beta-casein which were prestained for protein from Novex (San Diego, CA). As a positive control, lysates of cultured rabbit renal artery smooth muscle cells treated with 4 mM PMA for 18 hours and known to express MMP-2, -3 and -9 were added to each gel. After electrophoresis at 125 volts for 90 minutes, the gel was renatured in renaturing buffer from Novex (San Diego, CA) for 30 minutes. After equilibration in the Novex developing buffer (San Diego, CA) for 30 minutes, fresh developing buffer was added and the gelatin containing gel was allowed to develop overnight at 37°C while the casein containing gels were developed for 72 hours at 37°C to visualize the zymogen bands. The gelatin gels were stained with 0.5% Coomassie blue and destained with buffer consisting of 10% acetic acid, 50% methanol and 40% distilled water for 30 minutes to visualize the zymogen bands. An image of each gel was scanned into a computer with a Hewlett Packard scanner and the zymogen bands were quantified using Biosoft QuantiScan software, and the results were expressed in arbitrary densitometric units. Since on the casein impregnated gel MMP-1 and MMP-3 could not be differentiated because of similar electrophoretic mobility, the zymogen bands at 57 kD and 45 kD were considered to represent latent and active forms of both MMPs. An antibody specific for rabbit MMP-3 obtained from Calbiochem (La Jolla, CA) indicated by Western analysis that the zymogen bands at 57 kD and 45 kD contained MMP-3; however, the presence of MMP-1 could not be ruled out since a specific antibody to rabbit MMP-1 was not available. A faint band at 19 kD or MMP-7 was also observed in the casein gels; however, the band intensity precluded reproducible densitometric quantification. In order to validate that the zymogen bands were MMPs, 0.2 to 20 mM EDTA was added to the developing buffer of several control lanes. Catalytic activity was abolished upon incubation with EDTA;

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however, addition of 1 μ M avasimibe to the developing buffer had no effect on the formation of the zymogen bands (Figure 1).

Molecular Methods. Total RNA was extracted using a guanidine isothiocyanate method in both progression control and avasimibe-treated animals (n = 8/group). RNA (20 μ g) was electrophoresed in 1% formaldehyde/agarose gel and blotted onto a nylon membrane (S&S, Keene, NH) in 20 \times SSC by using capillary transfer overnight. The Northern blot was baked at 80°C for 20 minutes, UV-cross-linked, and prehybridized. Blots were hybridized at 65°C with a radiolabeled (α -³²P dCTP) cDNA probes for rabbit MMP-2, MMP-9, TIMP-1, TIMP-2 and, as an internal control, human S9 ribosomal cDNA (0.9 kb). The probes were generated by reverse transcriptase-polymerase chain reaction (RT-PCR) from rabbit tissue RNA using sense and antisense primers. The membranes were washed at 65°C in 1% SDS/2 \times SSC and quantified the signals using a Storm 860 phosphoimager and ImageQuant software (Molecular Dynamics, Sunnyvale, CA).

The rabbit-specific sense and antisense primers used above were prepared for MMP-1 (Fini M.E. et al., Biochemistry, 1987;26:6156-6165), MMP-2 (Matsumoto S. et al., Biochimica et Biophysica Acta, 1996;1307:137-139), MMP-3 (Fini M.E. et al., Arthritis and Rheumatism, 1987;30(11):1254-1264), MMP-9 (Tezuka K. et al., J. Biol. Chem., 1994;269:15006-15009), TIMP-1 (Wang, H. et al., Atherosclerosis, 1996;126:95-104), and TIMP-2 (Wertheimer S.J. and Katz S., Inflamm. Res., 1995;44(Suppl. 2):S121-S122) based on their respective GenBank published sequences. The custom primer sets for each MMP and TIMP were synthesized by Life Technologies, Inc. (Grand Island, NY). The criteria for both sense and antisense primer generation were a T_m range of 60°C to 80°C, scale of 50 nmol and desalted purity. These primer sets were used with a One-Step RT-PCR procedure in order to generate the PCR products used above for MMP-1 (1,200 bp), MMP-2 (500 bp), MMP-3 (700 bp), MP-9 (600 bp), TIMP-1 (650 bp), and TIMP-2 (600 bp).

Cytochemical Methods. For histologic evaluation of the iliac-femoral and aortic arch lesions, the first 1-cm segment of the iliac-femoral artery distal to the aortic-iliac bifurcation and ascending aorta distal to the aortic valves, respectively,

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were fixed in 10% neutral buffered formalin for 24 hours. The vessels were dehydrated, cleared in xylene, and infiltrated with molten paraffin (<60°C) using a Miles Scientific Tissue Tek VIP autoprocessor (Elkhart, IN). The tissue segments were embedded in paraffin and sectioned at 5 µm with a Reichert-Jung microtome purchased from Baxter (McGraw Park, IL). In order to obtain a thorough representation of the histologic appearance of the iliac-femoral lesion, 3 ribbons of 20 sections each were cut. Each ribbon of sections was spaced approximately 100 µm apart. Three pairs of sections, i.e., 1 pair from each ribbon, were affixed to cleaned 3-aminopropyltriethoxy-silane coated glass slides and stored until stained. The general histologic character and nature of the extracellular matrix was evaluated in hematoxylin and eosin and Verhoeff's elastica stained sections. The cellular composition of lesions was determined using anti-RAM11 antibody to rabbit monocyte-macrophages from DAKO (Carpinteria, CA) and anti-HHF35 smooth muscle cell antibody from ENZO Diagnostics (New York, NY). The immuno-cytochemical staining of monocyte-macrophages and SMC was performed as described previously.

Morphometric Methods. Sections of the iliac-femoral artery, a site of diet + chronic injury-induced atherosclerosis, and aortic arch, a reproducible and predictable site of hypercholesterolemia-induced lesions, stained using the Verhoeff's elastica procedure or with immunochemical markers for monocyte-macrophages were used for quantification of lesion and monocyte-macrophages areas as well as monocyte-macrophages size. Given the lack of a predictable site for atherosclerotic lesion formation in the descending thoracic aorta, no histologic measurements were made of lesions in this region. Gross extent of atherosclerosis within the thoracic aorta was also measured. The morphometric analyses of the iliac-femoral artery were performed on a Power Macintosh 8100/80AV computer using the public domain NIH Image program (written by Wayne Rasband at the US National Institute of Health and available from the Internet by anonymous ftp from zipper.nimh.nih.gov or on floppy disk from NTIS, 5285 Port Royal Road, Springfield, VA 22161, Part PB93-504868). Morphometric analyses of the aortic arch and thoracic aorta were performed using a PGT Imagist II image analysis system (Princeton, NJ) as previously described. Quantification of monocyte-

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macrophage size was performed on RAM-11 stained hematoxylin counterstained sections using Image Pro Plus image analysis software (Media Cybernetics, Silver Spring, MD). Images of ten random and non-overlapping fields of RAM-11 (+) areas within aortic arch cross-sections were collected at 40 X on a
5 Leica DMR microscope from each control and avasimibe-treated animal. Area of RAM-11 (+) staining and number of nuclei associated with the immunoprecipitate were quantified and average monocyte-macrophage cell area was calculated.

Iliac-femoral and aortic arch lesion and macrophage areas and aortic arch macrophage size were determined for each specimen, and the average per group
10 was calculated based on the mean specimen area. The percent lesion coverage of the thoracic aorta was also determined for each group.

Statistical Analyses. All statistical comparisons of the biochemical and morphometric data were made relative to the untreated hypercholesterolemic progression control. Total plasma cholesterol exposure of the animals over the
15 course of the study and during the drug treatment phase were determined by applying the trapezoidal rule to the cholesterol time curves. An analysis of variance procedure followed by a least significant difference test or 1-tailed Student's t-test for comparisons made relative to the untreated progression control were used. To ensure an unbiased result, the data were collected in a
20 double-blinded fashion. The specimens were ascribed to their respective treatment group after the biochemical and morphometric measurements were obtained.

In vivo studies were carried out which demonstrate the ability of the ACAT inhibitor, avasimibe, to directly limit macrophage accumulation in developing atherosclerotic plaques, resulting in mainly fibromuscular lesions.
25 Male New Zealand white rabbits were sequentially fed a cholesterol/fat diet for 9 weeks, fat only diet for 6 weeks and 25 mg/kg avasimibe for 7 to 8 weeks. Avasimibe had no effect on plasma total cholesterol exposure. Plasma avasimibe C_{max} and AUC_(0-24h) levels were 178 ng/mL and 2525 ng·h/mL, respectively, after 7 weeks of 25 mg/kg avasimibe. The IC₅₀ against human monocyte-
30 macrophage ACAT was 12 ng/mL when determined in the absence of albumin and aortic arch avasimibe levels were 25 ng/gm wet weight.

During the hypercholesterolemia phase, i.e., first 9 weeks of the study,

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plasma total cholesterol levels rose to between 1500 and 2000 mg/dL but decreased to approximately 500 mg/dL during the subsequent 6-week dietary normalization phase (Figure 2). At necropsy, mean plasma total cholesterol levels were reduced 70% by avasimibe; however, no significant changes were noted at previous time points. Prior to drug treatment, plasma total cholesterol exposure as measured by the area under the cholesterol time curve was similar between control and avasimibe groups, i.e., 117792 and 104422 mg·day/dL, respectively.

Avasimibe had no effect on plasma total cholesterol exposure during the final 8-week treatment phase (Figure 3). Plasma triglyceride levels were unaffected by avasimibe treatment and mean values ranged from between 46 and 169 mg/dL.

Plasma avasimibe C_{max} determined in a subset of animals treated with 25 mg/kg avasimibe for 7 weeks but comparably fed the fat diet was 178 (31) ng/mL (Mean ± %RSD) while the plasma AUC₍₀₋₂₄₎ was 2525 (33) ng·hr/mL. In extracts of aortic arch taken 24 hours post-dose after 8 weeks of receiving 25 mg/kg avasimibe, avasimibe concentrations were 25 ng/gm tissue wet weight.

In cultured human monocyte-macrophages, avasimibe reduced the intracellular CE concentration in a dose-dependent manner while free cholesterol and triglyceride concentrations were relatively unchanged over the range of 10 to 1000 nM avasimibe. The IC₅₀ of avasimibe against isolated cultured primary human monocyte-macrophage ACAT was 25 ± 9 nM or 12 ± 4.5 ng/mL (Mean ± SEM).

Thoracic aortic and iliac-femoral CE content were reduced 39% and 36%, respectively, by avasimibe relative to the untreated control and 25% and 39%, respectively, when compared to time zero, i.e., initiation of drug intervention (Table 1). Thoracic aortic free cholesterol content was reduced 39%; however, no change in total phospholipid content or free cholesterol was noted in the iliac-femoral artery.

Aortic arch MMP levels as measured by gelatin and casein zymography were reduced following avasimibe treatment (Figures 4 and 5). The density of the zymogen bands associated with 92 kD gelatinase (latent MMP-9) and 88 kD gelatinase (active MMP-9) was reduced 65% and 33%, respectively. Density of bands associated with 72 kD gelatinase (latent MMP-2) and 66 kD gelatinase

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(active MMP-2) were modestly reduced 7 to 20% but such changes were not statistically significant. Density of the zymogen bands on the casein gels associated with 52 kD (latent MMP-1 and -3) was reduced 52% and 45 kD (active MMP-1 and -3) was decreased 60% (Figure 6).

5 Cultured human monocyte-macrophage MMP levels as measured by gelatin zymography were unaffected by direct administration of avasimibe to the cultures. After a 24 hour incubation with 50 µg/mL acetyl-LDL, macrophage cholesteryl ester (CE) and free cholesterol (FC) content as determined by HPLC was 45% and 55% of the total cholesterol, respectively. Latent MMP-9 and
10 MMP-2 was present in differentiated non-CE enriched Hmdm and no change in the amount of catalytic activity was noted following incubation with acetyl-LDL for 24 hours. The catalytic activity was inhibited by incubation with EDTA. Direct incubation of up to 1000 nM avasimibe with cultured human monocyte-macrophages had no effect on latent MMP-9 and MMP-2 catalytic activity.

15 Changes in aortic arch MMP and TIMP expression as measured by Northern analysis were also noted upon avasimibe treatment (Figures 7 to 10 and Table 2). Aortic arch MMP-2 mRNA levels increased 135% while MMP-9, TIMP-1 and TIMP-2 mRNA levels decreased an average of 28% to 39% following avasimibe treatment.

20 Histologic evaluation of the aortic arch and iliac-femoral artery revealed that the atherosclerotic lesions were of several distinct morphologic appearances. In both vascular regions, the lesions were macrophage and SMC enriched; however, the relative distribution and quantity of these cell types varied. In the aortic arch, the macrophages were located both superficially and within the deep
25 intimal regions of the lesion while in the iliac-femoral artery the macrophages were predominantly deep intimal and medial. The degree of lesion complexity as evidenced by the incidence of fibrous plaques and fibrofoamy lesions varied with the vascular region and treatment group. Fibrous plaque lesions were identified as containing areas of basophilia and intimal necrosis, cholesterol clefts, and/or
30 calcium deposition. Fibrofoamy lesions were characterized as macrophage- and SMC-enriched lesions without evidence of intimal necrosis. In the aortic arch, 50% to 62% of the progression control and drug-treated animals had fibrous

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plaque lesions while 94% of the animals in the time zero group contained macrophage-enriched fibrofoamy lesions. In the iliac-femoral artery, avasimibe decreased the incidence of fibrous plaque lesions from 50% to 28% of the animals.

5 Morphometric measures of atherosclerotic lesion extent and composition were also altered. Relative to drug initiation, thoracic aortic, aortic arch, and iliac-femoral lesion size or extent and monocyte-macrophage enrichment increased in control animals administered the chow/fat diet alone. Avasimibe reduced the percent lesion coverage of the thoracic aorta from 34% in the control
10 animals to 20%. Avasimibe decreased the cross-sectional lesion area and monocyte-macrophage content of the aortic arch by 35% and 27%, respectively (Figure 11). Monocyte-macrophage size within the aortic arch was unaffected by avasimibe treatment (Table 3). In the iliac-femoral artery, avasimibe decreased the monocyte-macrophage content of the lesions by 77% and the ratio of RAM-11(+)
15 cell area/lesion area from 0.22 to 0.05 (Figure 12).

 Direct inhibition of arterial wall ACAT can potentially stabilize atherosclerotic lesions and prevent plaque rupture by limiting macrophage accumulation and reducing the expression of matrix metalloproteinases. This conclusion is supported by several findings of the current study which can be
20 summarized as follows: 1) avasimibe decreased the cross-sectional lesion area and monocyte-macrophage content of the foam cell enriched aortic arch by 35% and 27%, respectively. The reduction in monocyte-macrophage area reflected a change in cell number and not size. 2) In the iliac-femoral artery, avasimibe specifically decreased the monocyte-macrophage content of the lesions by 77%
25 and the ratio of RAM-11(+) cell area/lesion area from 0.22 to 0.05. 3) In the absence of a reduction in plasma cholesterol exposure, avasimibe decreased thoracic aortic and iliac-femoral CE content 39% and 36%, respectively. Since cholesteryl ester is the end product of the ACAT reaction, these data suggest that vascular ACAT was inhibited. 4) Plasma and tissue concentrations of avasimibe
30 were 178 ng/mL and 25 ng/gm weight wet, respectively. Such levels exceed that required to inhibit macrophage ACAT, i.e., $IC_{50} = 24$ nM or 12 ng/mL, and further support the hypothesis that direct inhibition of vascular ACAT had

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occurred. 5) Aortic arch MMP activity as measured zymographically was reduced 33% to 65% and aortic arch MMP-9, TIMP-1 and TIMP-2 mRNA levels were decreased 28% to 39%. Both groups of changes were associated with reductions in aortic arch macrophage area.

5 The studies support the assertion that inhibition of ACAT directly alters the progression of the fibrofoamy lesion by limiting their macrophage enrichment and expression of macrophage-derived pro-atherosclerotic molecules and, through lesion remodeling, by reducing the potential for plaque rupture associated with elaboration of macrophage-derived matrix metalloproteinases. In addition,
10 reductions in monocyte-macrophage accumulation within atherosclerotic lesions or alterations in the phenotype of the monocyte-macrophages further limits the expression of pro-atherosclerotic molecules.

 The studies described above show that macrophages are a source of MMPs and monocyte-macrophages and matrix degrading enzymes are localized to the
15 potentially friable shoulder regions of atherosclerotic lesions. They also show the significance of cholesteryl ester (CE) accumulation in macrophage foam cell formation and monocyte-macrophage recruitment. Thus, these studies provide the basis for the expectation that ACAT inhibitors *directly* limit macrophage accumulation in developing atherosclerotic plaques, resulting in mainly
20 fibromuscular lesions. Additionally, ACAT inhibitors prevent destabilization and/or rupture of pre-established atherosclerotic lesions by reducing MMP expression within the lesion.

 The compounds to be employed in the present invention can be prepared and administered in a wide variety of oral and parenteral dosage forms for treating
25 and preventing atherosclerosis. The compounds can be administered by injection, that is, intravenously, intramuscularly, intracutaneously, subcutaneously, intraduodenally, or intraperitoneally. Also, the compounds can be administered by inhalation, for example, intranasally. Additionally, the compounds can be administered transdermally. It will be obvious to those skilled in the art that the
30 following dosage forms may comprise as the active component, either a compound as a free base, acid, or a corresponding pharmaceutically acceptable salt of such compound. The active compound generally is present in a concentration of about 5% to about 95% by weight of the formulation.

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For preparing pharmaceutical compositions from the compounds of the present invention, pharmaceutically acceptable carriers can be either solid or liquid. Solid form preparations include powders, tablets, pills, capsules, cachets, suppositories, and dispersible granules. A solid carrier can be one or more
5 substances which may also act as diluents, flavoring agents, solubilizers, lubricants, suspending agents, binders, preservatives, tablet disintegrating agents, or an encapsulating material.

In powders, the carrier is a finely divided solid which is in a mixture with the finely divided active component.

10 In tablets, the active component is mixed with the carrier having the necessary binding properties in suitable proportions and compacted in the shape and size desired.

The powders and tablets preferably contain from 5% or 10% to about 70% of the active compound. Suitable carriers are magnesium carbonate, magnesium
15 stearate, talc, sugar, lactose, pectin, dextrin, starch, gelatin, tragacanth, methylcellulose, sodium carboxymethylcellulose, a low melting wax, cocoa butter, and the like. The term "preparation" is intended to include the formulation of the active compound with encapsulating material as a carrier providing a capsule in which the active component, with or without other carriers, is
20 surrounded by a carrier, which is thus in association with it. Similarly, cachets and lozenges are included. Tablets, powders, capsules, pills, cachets, and lozenges can be used as solid dosage forms suitable for oral administration.

For preparing suppositories, a low melting wax, such as a mixture of fatty acid glycerides or cocoa butter, is first melted and the active component is
25 dispersed homogeneously therein, as by stirring. The molten homogeneous mixture is then poured into convenient sized molds, allowed to cool, and thereby to solidify.

Liquid form preparations include solutions, suspensions, and emulsions, for example, water or water propylene glycol solutions. For parenteral injection,
30 liquid preparations can be formulated in solution in aqueous polyethylene glycol solution.

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Aqueous solutions suitable for oral use can be prepared by dissolving the active component in water and adding suitable colorants, flavors, stabilizing, and thickening agents as desired.

5 Aqueous suspensions suitable for oral use can be made by dispersing the finely divided active component in water with viscous material, such as natural or synthetic gums, resins, methylcellulose, sodium carboxymethylcellulose, and other well-known suspending agents.

Also included are solid form preparations which are intended to be converted, shortly before use, to liquid form preparations for oral administration.
10 Such liquid forms include solutions, suspensions, and emulsions. These preparations may contain, in addition to the active component, colorants, flavors, stabilizers, buffers, artificial and natural sweeteners, dispersants, thickeners, solubilizing agents, and the like.

The pharmaceutical preparation is preferably in unit dosage form. In such
15 form, the preparation is subdivided into unit doses containing appropriate quantities of the active component. The unit dosage form can be a packaged preparation, the package containing discrete quantities of preparation, such as packeted tablets, capsules, and powders in vials or ampoules. Also, the unit dosage form can be a capsule, tablet, cachet, or lozenge itself, or it can be the
20 appropriate number of any of these in packaged form.

The quantity of active component in a unit-dose preparation may be varied or adjusted from 1 to 1000 mg, preferably 10 to 100 mg according to the particular application and the potency of the active component. The composition can, if desired, also contain other compatible therapeutic agents.

25 The compounds utilized in the pharmaceutical method of this invention are administered at a dose that is effective to inhibit esterification activity of ACAT. Such effective amounts are those which prevent monocyte-macrophage accumulation. The compounds can also be used prophylactically at the same dose levels. The initial dosage of about 1 mg to about 100 mg per kilogram daily will
30 be effective to prevent and treat atherosclerosis. A daily dose range of about 5 to about 75 mg is preferred. The dosages, however, may be varied depending upon the requirements of the patient, the severity of the condition being treated, and the compound being employed. Determination of the proper dosage for a particular

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situation is within the skill of the art. Generally, treatment is initiated with smaller dosages which are less than the optimum dose of the compound. Thereafter, the dosage is increased by small increments until the optimum effect under the circumstance is reached. For convenience, the total daily dosage may be divided and administered in portions during the day if desired. Typical dosages will be from about 0.1 to about 500 mg/kg, and ideally about 25 to about 250 mg/kg.

The following examples illustrate typical formulations that can be utilized in the invention.

Tablet Formulation

Ingredient	Amount (mg)
ACAT Inhibiting Compound	25
Lactose	50
Cornstarch (for mix)	10
Cornstarch (paste)	10
Magnesium stearate (1%)	5
Total	100

The ACAT inhibitor, lactose, and cornstarch (for mix) are blended to uniformity. The cornstarch (for paste) is suspended in 200 mL of water and heated with stirring to form a paste. The paste is used to granulate the mixed powders. The wet granules are passed through a No. 8 hand screen and dried at 80°C. The dry granules are lubricated with the 1% magnesium stearate and pressed into a tablet. Such tablets can be administered to a human from 1 to 4 times a day for prevention of atherosclerotic plaque destabilization and/or rupture.

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Preparation for Oral Solution

Ingredient	Amount
ACAT Inhibiting Compound	400 mg
Sorbitol solution (70% N.F.)	40 mL
Sodium benzoate	20 mg
Saccharin	5 mg
Red dye	10 mg
Cherry flavor	20 mg
Distilled water q.s.	100 mL

5 The sorbitol solution is added to 40 mL of distilled water, and the ACAT inhibitor is dissolved therein. The saccharin, sodium benzoate, flavor, and dye are added and dissolved. The volume is adjusted to 100 mL with distilled water. Each milliliter of syrup contains 4 mg of invention compound.

Parenteral Solution

10 In a solution of 700 mL of propylene glycol and 200 mL of water for injection is suspended 20 g of avasimibe. After suspension is complete, the pH is adjusted to 6.5 with 1N sodium hydroxide, and the volume is made up to 1000 mL with water for injection. The formulation is sterilized, filled into 5.0 mL ampoules each containing 2.0 mL, and sealed under nitrogen.

Table 1. Thoracic Aortic and Iliac-Femoral Lipid Content

Treatment	Thoracic Aorta ^a			Iliac-Femoral Artery ^a		
	Cholesteryl Ester	Free Cholesterol	Total Phospholipids	Cholesteryl Ester	Free Cholesterol	Total Phospholipids
Time Zero Control	148.1 ± 20.7	57.9 ± 6.3	49.9 ± 3.0	181.0 ± 20.8	56.9 ± 3.8	39.3 ± 3.1
Progression Control	179.7 ± 17.7	84.9 ± 8.8	63.6 ± 5.0	170.6 ± 13.4	56.7 ± 6.3	38.6 ± 2.7
Avasimibe (25 mg/kg)	110.6 ± 19.4* (-39)	51.7 ± 11.4* (-39)	56.2 ± 6.6 (-12)	110.1 ± 16.4* (-36)	51.3 ± 6.4 (-10)	35.9 ± 7.0 (-7)

N = 16 in the time zero and progression group and 8 in the avasimibe treatment group. Value in parentheses represents percent change from progression control.

* Statistically significant difference from the progression control at $p < 0.05$

^a Data are expressed as mean ± SEM in µg/mg dry defatted tissue.

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Table 2. MMP and TIMP mRNA Levels in Aortic Arch of Control and Avasimibe-Treated Animals

	Progression Control	Avasimibe (25 mg/kg)
MMP-2	1.11 ± 0.27	2.61 ± 0.26*
MMP-9	1.33 ± 0.35	0.96 ± 0.14
TIMP-1	1.57 ± 0.42	1.11 ± 0.21
TIMP-2	1.22 ± 0.08	0.88 ± 0.03*

The data have been normalized for loading of the gel based on S9 content and are expressed as Mean ± SEM, n = 8/group.

* Statistically significant difference from the progression control at p <0.05.

Table 3. Aortic Arch Monocyte-Macrophage Size

Treatment	Average Macrophage Size (μm) ^a
Time Zero Control	362 ± 41
Progression Control	300 ± 26
Avasimibe (25 mg/kg)	281 ± 30

N = 16 in the time zero and progression group and 8 in the avasimibe treatment group.

^a Data are expressed as mean ± SEM. No statistically significant differences in average macrophage size were noted at p <0.05.

FIGURES

Figures are provided to illustrate data in various visual formats.

In brief:

5 Figure 1 is a gelatin zymography showing avasimibe failed to inhibit MMP-2 and -9 and a casein zymography showing avasimibe failed to inhibit MMP-1 or -3 versus untreated controls.

10 Figure 2 is a line graph with error bars showing mean plasma total cholesterol levels over the time course of the study for drug-treated animals versus untreated progression controls. In both groups, plasma total cholesterol levels rose during the hypercholesterolemia phase of the study (Week 0 to Week 9), then decreased during the subsequent 6-week dietary normalization phase (Week 9 to Week 15).

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Figure 3 is a bar graph showing mean plasma cholesterol exposure during the final 7-week treatment phase of the study. Avasimibe had no effect on plasma total cholesterol levels during Weeks 15 to 22 relative to untreated progression controls.

5 Figure 4 is a gelatin zymography showing MMP-2 and -9 expression in the aortic arch of hypercholesterolemic rabbits treated with 25 mg/kg of avasimibe. MMP-2 and -9 levels were reduced relative to untreated progression controls.

 Figure 5 is a casein zymography showing MMP-1 or -3 expression in the aortic arch of hypercholesterolemic rabbits treated with 25 mg/kg of avasimibe.
10 MMP-1 or -3 levels were reduced relative to untreated progression controls.

 Figure 6 is a bar graph showing mean densitometry measurements of the latent and active zymogen bands of the MMP-9, -2, and -1 and -3. Reduction in levels of latent and active forms of MMP-9 and -1 and -3 were statistically significant while those for MMP-2 were not compared to untreated progression
15 controls.

 Figure 7 is a Northern blot of MMP-2 mRNA expression in the aortic arch. Aortic arch MMP-2 mRNA levels increased in avasimibe-treated animals versus untreated progression controls.

 Figure 8 is a Northern blot of MMP-9 mRNA expression in the aortic arch.
20 Aortic arch MMP-9 mRNA levels decreased in avasimibe-treated animals versus untreated progression controls.

 Figure 9 is a Northern blot of MMP-1 mRNA expression in the aortic arch. Aortic arch TIMP-1 mRNA levels decreased in avasimibe-treated animals versus untreated progression controls.

25 Figure 10 is a Northern blot of TIMP-2 mRNA expression in the aortic arch. Aortic arch TIMP-2 mRNA levels decreased in avasimibe-treated animals versus untreated progression controls.

 Figure 11 is a bar graph depicting a morphometric evaluation of the extent of atherosclerosis within the thoracic aorta and the cross-sectional lesion and
30 macrophage area within the aortic arch. Relative to drug initiation, thoracic aortic, aortic arch, and iliac-femoral lesion size or extent and monocyte-macrophage enrichment increased in untreated progression control animals administered the chow/fat diet alone.

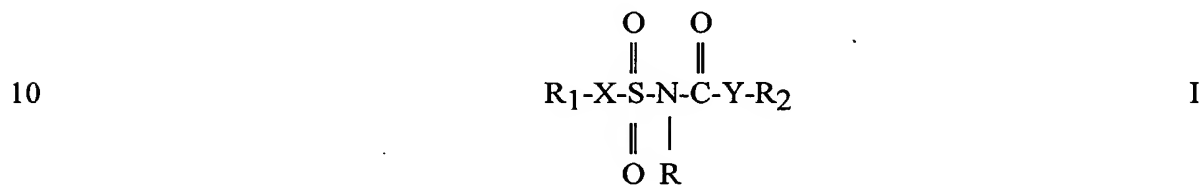
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Figure 12 is a bar graph depicting a morphometric evaluation of the iliac-femoral cross-section lesion and macrophage area. Avasimibe decreased the monocyte-macrophage content of the lesions and the ratio of RAM-11(+) cell area/lesion area relative to untreated progression controls.

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CLAIMS

1. A method of inhibiting monocyte-macrophage accumulation in atherosclerotic lesions in a mammal, including the human, in need of such treatment comprising administering to said mammal a therapeutically effective amount of an ACAT inhibitor.
2. A method according to Claim 1 wherein the compound is a compound of formula



or a pharmaceutically acceptable salt thereof wherein:

- X and Y are selected from oxygen, sulfur and $(\text{CR}'\text{R}'')_n$ wherein n is an integer of from 1 to 4 and R' and R'' are each independently hydrogen, C₁-C₆ alkyl, C₁-C₆ alkoxy, halogen, hydroxy, C₂-C₆ acyloxy, C₃-C₁₀ cycloalkyl, phenyl optionally substituted or R' and R'' together form a C₃-C₁₀ cycloalkyl or a carbonyl;

R is hydrogen, a straight or branched alkyl of from 1 to 8 carbon atoms or benzyl;

R₁ and R₂ are each independently selected from

- (a) phenyl or phenoxy each of which is unsubstituted or is substituted with 1 to 5 substituents selected from
- phenyl,
 - an alkyl group having from 1 to 6 carbon atoms and which is straight or branched,
 - an alkoxy group having from 1 to 6 carbon atoms and which is straight or branched;
 - phenoxy,

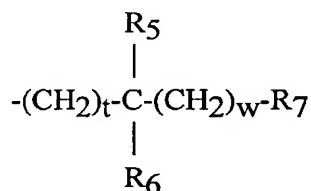
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- hydroxy,
fluorine,
chlorine,
bromine,
5 nitro,
trifluoromethyl,
-COOH,
-COOalkyl wherein alkyl has from 1 to 4 carbon atoms and
is straight or branched,
10 -(CH₂)_pNR₃R₄ wherein p is zero or 1, and each of R₃ and
R₄ is selected from hydrogen or a straight or
branched alkyl group having 1 to 4 carbon atoms;
(b) 1- or 2-naphthyl unsubstituted or substituted with from 1 to
3 substituents selected from
15 phenyl,
an alkyl group having from 1 to 6 carbon atoms and which
is straight or branched,
an alkoxy group having from 1 to 6 carbon atoms and
which is straight or branched;
20 hydroxy,
phenoxy,
fluorine,
chlorine,
bromine,
25 nitro,
trifluoromethyl,
-COOH,
-COOalkyl wherein alkyl has from 1 to 4 carbon atoms and
is straight or branched,
30 -(CH₂)_pNR₃R₄ wherein p, R₃ and R₄ have the meanings
defined above;
(c) arylalkyl;

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- (d) a straight or branched alkyl chain having from 1 to 20 carbon atoms and which is saturated or contains from 1 to 3 double bonds;
or
(e) adamantyl or a cycloalkyl group wherein the cycloalkyl moiety has from 3 to 10 carbon atoms.

3. A method according to Claim 1 wherein
R₁ and R₂ are independently selected from substituted phenyl or



wherein t and w are independently an integer of from 0 to 4 with the proviso that the sum of t and w is not greater than 5; R₅ and R₆ are each independently selected from hydrogen or alkyl having from 1 to 6 carbon atoms, or when R₅ is hydrogen, R₆ can be selected from the groups defined for R₇; and R₇ is phenyl or phenyl substituted with from 1 to 3 substituents selected from a straight or branched alkyl group having from 1 to 6 carbon atoms, straight or branched alkoxy group having from 1 to 6 carbon atoms, phenoxy, hydroxy, fluorine, chlorine, bromine, nitro, trifluoromethyl, -COOH, -COOalkyl, wherein alkyl has from 1 to 4 carbon atoms, or -(CH₂)_pNR₃R₄;

X is oxygen;

Y is (CR'R'')_n; and

R is hydrogen

wherein n is an integer of 1 or 2, and substituted phenyl, p, R₃, R₄, R', and R'' have the meanings as defined above in Claim 2.

4. A method according to Claim 1 wherein the compound administered is selected from

Sulfamic acid (phenylacetyl)-2,6-bis(1-methylethyl)phenyl ester,

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- Sulfamic acid [[2,6-bis(1-methylethyl)phenyl]acetyl]-
2,6-bis(1-methylethyl)phenyl ester,
- Sulfamic acid [[2,4,6-tris(1-methylethyl)phenyl]acetyl]-
2,4,6-tris(1-methylethyl)phenyl ester,
- 5 Sulfamic acid [[2,6-bis(1-methylethyl)phenyl]acetyl]-
2,4,6-tris(1-methylethyl)phenyl ester,
- Sulfamic acid [adamantaneacetyl]-2,6-bis(1-methylethyl)phenyl
ester,
- Sulfamic acid [[2,6-bis(1-methylethyl)phenyl]acetyl]-
10 2,6-bis(1-methylethyl)phenyl ester-sodium salt,
- Sulfamic acid [[2,4,6-tris(1-methylethyl)phenyl]acetyl]-
2,6-bis(1-methylethyl)phenyl ester-sodium salt,
- Sulfamic acid (decanoyl)-2,6-bis-(1-methylethyl)phenyl ester,
- Sulfamic acid (dodecanoyl)-2,6-bis-(1-methylethyl)phenyl ester,
- 15 2,6-Bis(1-methylethyl)-N-[[[2,4,6-tris(1-methylethyl)phenyl]-
methyl]sulfonyl]benzeneacetamide,
- 2,6-Bis(1-methylethyl)-N-[[[2,4,6-tris(1-methylethyl)phenyl]-
methyl]sulfonyl]benzeneacetamide-sodium salt,
- 2,6-Bis(1-methylethyl)phenyl[[[2,4,6-tris(1-methylethyl)phenyl]-
20 methyl]sulfonyl]carbamate,
- 2,6-Bis(1-methylethyl)phenyl[[[2,4,6-tris(1-methylethyl)phenyl]-
methyl]sulfonyl]carbamate-sodium salt,
- Sulfamic acid (1-oxo-3,3-diphenylpropyl)-2,6-bis(1-
methylethyl)phenyl ester,
- 25 Sulfamic acid [2,6-dichlorophenyl(acetyl)]-2,6-bis(1-
methylethyl)phenyl ester,
- Sulfamic acid [2,6-dichlorophenyl(acetyl)]-2,6-bis(1-
methylethyl)phenyl ester,
- Sulfamic acid trans-[(2-phenylcyclopropyl)carbonyl]-
30 2,6-bis(1-methylethyl)phenyl ester,
- Sulfamic acid [2,5-dimethoxyphenyl(acetyl)]-2,6-bis(1-
methylethyl)phenyl ester,

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Sulfamic acid [2,4,6-trimethoxyphenyl(acetyl)]-2,6-bis(1-methylethyl)phenyl ester,

Sulfamic acid [2,4,6-trimethylphenyl(acetyl)]-2,6-bis(1-methylethyl)phenyl ester,

5 Sulfamic acid [2-thiophenyl(acetyl)]-2,6-bis(1-methylethyl)phenyl ester,

Sulfamic acid [3-thiophenyl(acetyl)]-2,6-bis(1-methylethyl)phenyl ester,

10 Sulfamic acid [2-methoxyphenyl(acetyl)]-2,6-bis(1-methylethyl)phenyl ester,

Sulfamic acid (oxophenylacetyl)-2,6-bis(1-methylethyl)phenyl ester,

Sulfamic acid [2-trifluoromethylphenyl(acetyl)]-2,6-bis(1-methylethyl)phenyl ester,

15 Sulfamic acid (1-oxo-2-phenylpropyl)-2,6-bis(1-methylethyl)phenyl ester,

Sulfamic acid (cyclopentylphenylacetyl)-2,6-bis(1-methylethyl)phenyl ester,

20 Sulfamic acid (cyclohexylacetyl)-2,6-bis(1-methylethyl)phenyl ester,

Sulfamic acid (diphenylacetyl)-2,6-bis(1-methylethyl)phenyl ester,

Sulfamic acid (triphenylacetyl)-2,6-bis(1-methylethyl)phenyl ester,

Sulfamic acid [(1-phenylcyclopentyl)carbonyl]-2,6-bis(1-methylethyl)phenyl ester,

25 Sulfamic acid (3-methyl-1-oxo-2-phenylpentyl)-2,6-bis(1-methylethyl)phenyl ester,

Sulfamic acid (1-oxo-2-phenylbutyl)-2,6-bis(1-methylethyl)phenyl ester,

30 Sulfamic acid (cyclohexylphenylacetyl)-2,6-bis(1-methylethyl)phenyl ester,

Sulfamic acid (1-oxo-2,2-diphenylpropyl)-2,6-bis(1-methylethyl)phenyl ester,

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Sulfamic acid [(9H-fluoren-9-yl)carbonyl]-2,6-bis(1-methylethyl)phenyl ester,

Sulfamic acid (1-oxo-3-phenylpropyl)-2,6-bis(1-methylethyl)phenyl ester,

5 Sulfamic acid [1-oxo-3-[2,4,6-tris(1-methylethyl)phenyl]-2-propenyl]-2,6-bis(1-methylethyl)phenyl ester,

Sulfamic acid [1-oxo-3-[2,4,6-tris(1-methylethyl)phenyl]propyl]-2,6-bis(1-methylethyl)phenyl ester,

10 Sulfamic acid [(acetyloxy)[2,4,6-tris(1-methylethyl)phenyl]acetyl]-2,6-bis(1-methylethyl)phenyl ester,

Sulfamic acid [hydroxy[2,4,6-tris(1-methylethyl)phenyl]acetyl]-2,6-bis(1-methylethyl)phenyl ester,

Sulfamic acid [fluoro[2,4,6-tris(1-methylethyl)phenyl]acetyl]-2,6-bis(1-methylethyl)phenyl ester,

15 Sulfamic acid (3-methyl-1-oxo-2-phenylpentyl)-2,6-bis(1-methylethyl)phenyl ester sodium salt,

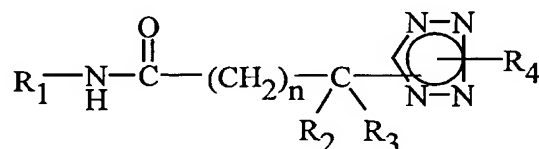
Sulfamic acid [[2,4,6-tris(1-methylethyl)phenoxy]acetyl]-2,6-bis(1-methylethyl)phenyl ester,

20 Sulfamic acid [[2,6-bis(1-methylethyl)phenoxy]acetyl]-2,6-bis(1-methylethyl)phenyl ester, and

Sulfamic acid [[2,4,6-tris(1-methylethyl)phenyl]acetyl]-2,6-bis(phenyl)phenyl ester.

5. A method according to Claim 1 wherein the compound administered is sulfamic acid, [[2,4,6-tris(1-methylethyl)phenyl]acetyl]-2,6-bis(1-methylethyl)phenyl ester.

6. A method according to Claim 1 wherein the compound is a compound of formula



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wherein n is 0, 1, or 2;

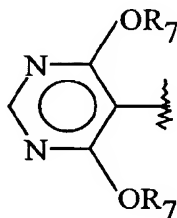
R₁ is selected from:

- 5 (a) phenyl which is unsubstituted or is substituted with from 1 to 3 substituents selected from:
- alkyl having from 1 to 4 carbon atoms and which is straight or branched,
- alkoxy having from 1 to 3 carbon atoms and which is straight or branched,
- 10 alkylthio having from 1 to 3 carbon atoms and which is straight or branched,
- hydroxy,
- phenyl,
- fluorine,
- chlorine,
- 15 bromine,
- nitro,
- cyano,
- trifluoromethyl,
- COOH,
- 20 -COOalkyl wherein alkyl has from 1 to 4 carbon atoms and which is straight or branched,
- (CH₂)_m NR₅ R₆ wherein m is zero or 1, and each of R₅ and R₆ is hydrogen or a straight or branched alkyl group having 1 to 4 carbon atoms;
- 25 (b) 1- or 2-naphthyl which is unsubstituted or substituted with 1 to 3 substituents selected from:
- alkyl having from 1 to 4 carbon atoms and which is straight or branched,
- alkoxy having from 1 to 3 carbon atoms and which is straight or branched,
- 30 hydroxy,
- fluorine,

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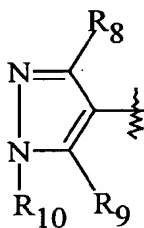
chlorine,
bromine,
nitro,
cyano,
5 trifluoromethyl,
-COOH,
-COOalkyl wherein alkyl has from 1 to 4 carbon atoms and is
straight or branched,
-(CH₂)_m NR₅ R₆ wherein m, R₅, and R₆ have the meanings
10 defined above;

(c) the group



wherein R₇ is a lower alkyl group having from 1 to 3 carbon atoms
and is straight or branched;

15 (d) the group

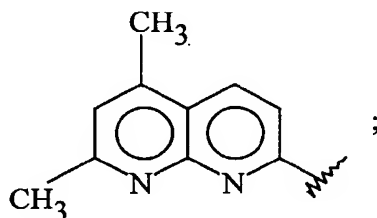


wherein R₈ and R₉ are straight or branched alkyl having from 1 to
4 carbon atoms or phenyl, and R₁₀ is a straight or branched
hydrocarbon group having from 1 to 18 carbon atoms
20 which is saturated or is unsaturated containing 1 double
bond or 2 nonadjacent double bonds; phenyl; phenyl
substituted with from 1 to 3 substituents selected from
straight or branched alkyl having 1 to 4 carbon atoms,
straight or branched alkoxy having from 1 to 3 carbon

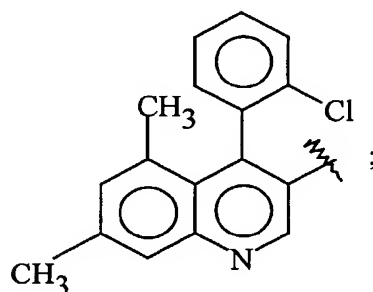
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atoms, hydroxy, fluorine, chlorine, bromine, nitro, cyano, trifluoromethyl, -COOH, -COOalkyl wherein alkyl has from 1 to 4 carbon atoms and is straight or branched or $-(CH_2)_mNR_5R_6$ wherein m, R_5 , and R_6 are as defined above; or a heteroaryl group selected from 2-, 3-, or 4-pyridyl, 2-, 4-, or 5-pyrimidinyl, 2- or 3-pyrazinyl, 2-, 3-, 4-, 5-, 6-, 7-, or 8-quinolinyl, or 3- or 4-pyridazinyl and the N-oxides thereof;

(e) the group



(f) the group



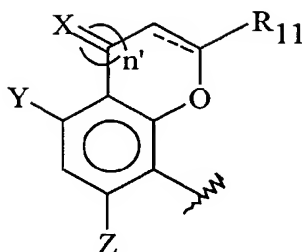
(g) a straight or branched hydrocarbon group having from 1 to 18 carbon atoms which is saturated or is unsaturated containing one double bond or 2 nonadjacent double bonds;

(h) a cycloalkyl group having from 3 to 8 carbon atoms;

(i) a heteroaryl group selected from 2-, 3-, or 4-pyridyl which is unsubstituted or substituted with an alkyl group having from 1 to 4 carbon atoms or 2-, 4-, or 5-pyrimidinyl, and the N-oxides thereof;

(j) the group

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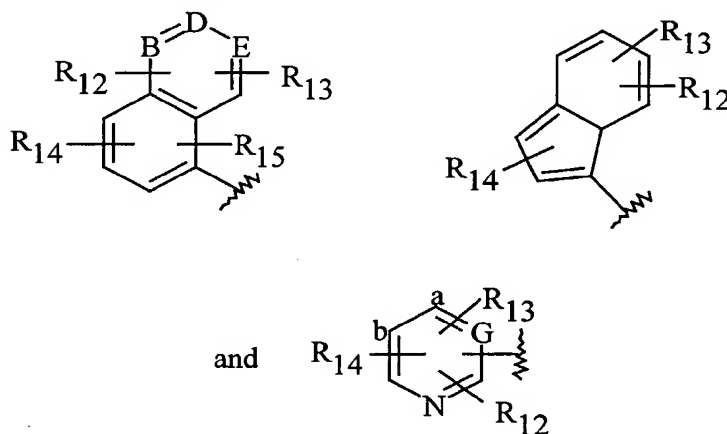


wherein --- denotes a single or double bond; Y and Z are each independently hydrogen, a straight or branched alkyl group of 1 to 4 carbon atoms, an alkoxy group of 1 to 3 carbon atoms or halogen;

X is oxygen or 2 hydrogen atoms;

R₁₁ is hydrogen or a straight or branched alkyl group of 1 to 4 carbon atoms, and n' is zero or 1; or

(k) is selected from the group



wherein R₁₂, R₁₃, R₁₄, and R₁₅ are each independently hydrogen, halogen, a straight or branched alkyl group of 1 to 4 carbon atoms, an alkoxy group of 1 to 3 carbon atoms, and alkylthio group of 1 to 3 carbon atoms, cycloalkylthio of 5 to 7 carbon atoms, phenylalkylthio in which the alkylene is from 1 to 4 carbon atoms, substituted phenylthio, heteroarylthio, or heteroaryloxy; and B, D, E, and G are nitrogen or carbon where one or more of B, D, and E is nitrogen; with the proviso that when G = nitrogen the group

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is attached to the nitrogen atom of Formula I at the 4- or 5-position of the pyrimidine ring (a or b);

wherein R₂ and R₃ are the same or different and are selected from:

- (a) hydrogen, halogen or one of R₂ or R₃ is hydroxy;
- 5 (b) a straight or branched alkyl group having from 1 to 12 carbon atoms, or a cycloalkyl group having from 3 to 8 carbon atoms;
- (c) a phenyl or phenylalkyl group where the alkylene is from 1 to 4 carbon atoms and which the phenyl ring
10 unsubstituted or substituted with from 1 to 3 substituents selected from straight or branched alkyl having from 1 to 4 carbon atoms, straight or branched alkoxy having from 1 to 4 carbon atoms, alkythio, straight or branched having 1 to 4 carbon
15 atoms, hydroxy, fluorine, chlorine, bromine, trifluoromethyl, cyano, nitro, phenyl, or (CH₂)_mNR₅R₆ wherein m, R₅, and R₆ have the meanings defined above;
- (d) a straight or branched alkenyl group having from
20 2 to 6 carbon atoms; or
- (e) R₂ and R₃ taken together with the carbon atom to which they are attached form an alkylidene group of 1 to 4 carbon atoms, a benzylidene group, or a cycloalkyl group having from 3 to 7 carbon atoms;
25 or
- (f) when R₂ is hydrogen, F, alkyl of C₁₋₁₂ atoms, R₃ is a heteroaryl selected from a 5- or 6-membered monocyclic or fused bicyclic group containing at least 1 to 4 heteroatoms in at least one ring, said
30 heteroatoms being nitrogen, oxygen, or sulfur and combinations thereof, said heteroaryl group being unsubstituted or substituted with an alkyl group

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having from 1 to 4 carbon atoms and the N-oxides thereof;

- (g) 1- or 2-naphthyl which is unsubstituted or substituted with 1 to 3 substituents selected from:
alkyl having from 1 to 4 carbon atoms and which is straight or branched,
alkoxy having from 1 to 3 carbon atoms and which is straight or branched;

wherein R₄ is a straight or branched hydrocarbon chain having

from 1 to 20 carbon atoms and is saturated or is unsaturated and has 1 double bond or has 2 nonadjacent double bonds or is alkylthio having 1 to 20 carbon atoms and is saturated; or a pharmaceutically acceptable salt or individual enantiomeric isomer thereof.

7. A method according to Claim 1 wherein the compound administered is selected from
- (±) 2-dodecyl- α -phenyl-N-(2,4,6-trimethoxyphenyl)-2H-tetrazole-5-acetamide,
- (±) 2-dodecyl-N, α -diphenyl-2H-tetrazole-5-acetamide,
- (±)-N-[2,6-bis(1-methylethyl)phenyl]-2-dodecyl- α -phenyl-2H-tetrazole-5-acetamide,
- (±)-N-(2,4-difluorophenyl)-2-dodecyl- α -phenyl-2H-tetrazole-5-acetamide,
- (±)-2-octyl- α -phenyl-N-(2,4,6-trimethoxyphenyl)-2H-tetrazole-5-acetamide, or
- (±)-2-hexadecyl- α -phenyl-N-(2,4,6-trimethoxyphenyl)-2H-tetrazole-5-acetamide.
8. A method according to Claim 1 wherein the compound administered is selected from

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(±)-N-[2,6-Bis(1-methylethyl)phenyl]-2-(2-dodecyl-2*H*-tetrazol-5-yl)-2-phenyl-acetamide,

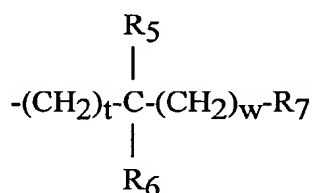
(+)-N-[2,6-Bis(1-methylethyl)phenyl]-2-(2-dodecyl-2*H*-tetrazol-5-yl)-2-phenyl-acetamide, or

5 (-)-N-[2,6-Bis(1-methylethyl)phenyl]-2-(2-dodecyl-2*H*-tetrazol-5-yl)-2-phenyl-acetamide.

9. A method of inhibiting expression of matrix metalloproteinases in atherosclerotic lesions in a mammal, including the human, in need of such treatment comprising administering to said mammal a therapeutically effective amount of an ACAT inhibitor.

10. A method according to Claim 9 of inhibiting expression of matrix metalloproteinases in atherosclerotic lesions in a mammal, including the human, in need thereof comprising administering to said mammal an effective amount of a compound of Formula I above.

11. A method according to Claim 9 wherein R₁ and R₂ are independently selected from substituted phenyl or



wherein t and w are independently an integer of from 0 to 4 with the proviso that the sum of t and w is not greater than 5; R₅ and R₆ are each independently selected from hydrogen or alkyl having from 1 to 6 carbon atoms, or when R₅ is hydrogen, R₆ can be selected from the groups defined for R₇; and R₇ is phenyl or phenyl substituted with from 1 to 3 substituents selected from a straight or branched alkyl group having from 1 to 6 carbon atoms, straight or branched alkoxy group having from 1 to 6 carbon atoms, phenoxy, hydroxy, fluorine, chlorine, bromine, nitro, trifluoromethyl,

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-COOH, -COOalkyl, wherein alkyl has from 1 to 4 carbon atoms,
or $-(CH_2)_pNR_3R_4$;

X is oxygen;

Y is $(CR'R'')_n$; and

5 R is hydrogen

wherein n is an integer of 1 or 2, and substituted phenyl, p, R_3 , R_4 , R' , and
 R'' have the meanings as defined above in Claim 10.

12. A method according to Claim 9 wherein the compound administered is
selected from

- 10 Sulfamic acid (phenylacetyl)-2,6-bis(1-methylethyl)phenyl ester,
Sulfamic acid[[2,6-bis(1-methylethyl)phenyl]acetyl]-
2,6-bis(1-methylethyl)phenyl ester,
Sulfamic acid [[2,4,6-tris(1-methylethyl)phenyl]acetyl]-
2,4,6-tris(1-methylethyl)phenyl ester,
15 Sulfamic acid[[2,6-bis(1-methylethyl)phenyl]acetyl]-
2,4,6-tris(1-methylethyl)phenyl ester,
Sulfamic acid[adamantaneacetyl]-2,6-bis(1-methylethyl)phenyl
ester,
Sulfamic acid[[2,6-bis(1-methylethyl)phenyl]acetyl]-
20 2,6-bis(1-methylethyl)phenyl ester-sodium salt,
Sulfamic acid[[2,4,6-tris(1-methylethyl)phenyl]acetyl]-
2,6-bis(1-methylethyl)phenyl ester-sodium salt,
Sulfamic acid (decanoyl)-2,6-bis-(1-methylethyl)phenyl ester,
Sulfamic acid (dodecanoyl)-2,6-bis-(1-methylethyl)phenyl ester,
25 2,6-Bis(1-methylethyl)-N-[[[2,4,6-tris(1-methylethyl)phenyl]-
methyl]sulfonyl]benzeneacetamide,
2,6-Bis(1-methylethyl)-N-[[[2,4,6-tris(1-methylethyl)phenyl]-
methyl]sulfonyl]benzeneacetamide-sodium salt,
2,6-Bis(1-methylethyl)phenyl[[[2,4,6-tris(1-methylethyl)phenyl]-
30 methyl]sulfonyl]carbamate,

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2,6-Bis(1-methylethyl)phenyl[[[2,4,6-tris(1-methylethyl)phenyl]-methyl]sulfonyl]carbamate-sodium salt,

Sulfamic acid (1-oxo-3,3-diphenylpropyl)-2,6-bis(1-methylethyl)phenyl ester,

5 Sulfamic acid [2,6-dichlorophenyl(acetyl)]-2,6-bis(1-methylethyl)phenyl ester,

Sulfamic acid [2,6-dichlorophenyl(acetyl)]-2,6-bis(1-methylethyl)phenyl ester,

10 Sulfamic acid trans-[(2-phenylcyclopropyl)carbonyl]-2,6-bis(1-methylethyl)phenyl ester,

Sulfamic acid [2,5-dimethoxyphenyl(acetyl)]-2,6-bis(1-methylethyl)phenyl ester,

Sulfamic acid [2,4,6-trimethoxyphenyl(acetyl)]-2,6-bis(1-methylethyl)phenyl ester,

15 Sulfamic acid [2,4,6-trimethylphenyl(acetyl)]-2,6-bis(1-methylethyl)phenyl ester,

Sulfamic acid [2-thiophenyl(acetyl)]-2,6-bis(1-methylethyl)phenyl ester,

20 Sulfamic acid [3-thiophenyl(acetyl)]-2,6-bis(1-methylethyl)phenyl ester,

Sulfamic acid [2-methoxyphenyl(acetyl)]-2,6-bis(1-methylethyl)phenyl ester,

Sulfamic acid (oxophenylacetyl)-2,6-bis(1-methylethyl)phenyl ester,

25 Sulfamic acid [2-trifluoromethylphenyl(acetyl)]-2,6-bis(1-methylethyl)phenyl ester,

Sulfamic acid (1-oxo-2-phenylpropyl)-2,6-bis(1-methylethyl)phenyl ester,

30 Sulfamic acid (cyclopentylphenylacetyl)-2,6-bis(1-methylethyl)phenyl ester,

Sulfamic acid (cyclohexylacetyl)-2,6-bis(1-methylethyl)phenyl ester,

Sulfamic acid (diphenylacetyl)-2,6-bis(1-methylethyl)phenyl ester,

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Sulfamic acid (triphenylacetyl)-2,6-bis(1-methylethyl)phenyl ester,

Sulfamic acid [(1-phenylcyclopentyl)carbonyl]-2,6-bis(1-methylethyl)phenyl ester,

5 Sulfamic acid (3-methyl-1-oxo-2-phenylpentyl)-2,6-bis(1-methylethyl)phenyl ester,

Sulfamic acid (1-oxo-2-phenylbutyl)-2,6-bis(1-methylethyl)phenyl ester,

Sulfamic acid (cyclohexylphenylacetyl)-2,6-bis(1-methylethyl)phenyl ester,

10 Sulfamic acid (1-oxo-2,2-diphenylpropyl)-2,6-bis(1-methylethyl)phenyl ester,

Sulfamic acid [(9H-fluoren-9-yl)carbonyl]-2,6-bis(1-methylethyl)phenyl ester,

15 Sulfamic acid (1-oxo-3-phenylpropyl)-2,6-bis(1-methylethyl)phenyl ester,

Sulfamic acid [1-oxo-3-[2,4,6-tris(1-methylethyl)phenyl]-2-propenyl]-2,6-bis(1-methylethyl)phenyl ester,

Sulfamic acid [1-oxo-3-[2,4,6-tris(1-methylethyl)phenyl]propyl]-2,6-bis(1-methylethyl)phenyl ester,

20 Sulfamic acid [(acetyloxy)[2,4,6-tris(1-methylethyl)phenyl]acetyl]-2,6-bis(1-methylethyl)phenyl ester,

Sulfamic acid [hydroxy[2,4,6-tris(1-methylethyl)phenyl]acetyl]-2,6-bis(1-methylethyl)phenyl ester,

25 Sulfamic acid [fluoro[2,4,6-tris(1-methylethyl)phenyl]acetyl]-2,6-bis(1-methylethyl)phenyl ester,

Sulfamic acid (3-methyl-1-oxo-2-phenylpentyl)-2,6-bis(1-methylethyl)phenyl ester sodium salt,

Sulfamic acid [[2,4,6-tris(1-methylethyl)phenoxy]acetyl]-2,6-bis(1-methylethyl)phenyl ester,

30 Sulfamic acid [[2,6-bis(1-methylethyl)phenoxy]acetyl]-2,6-bis(1-methylethyl)phenyl ester, and

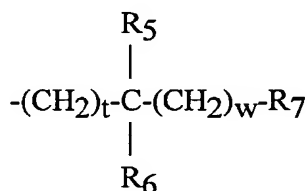
Sulfamic acid [[2,4,6-tris(1-methylethyl)phenyl]acetyl]-2,6-bis(phenyl)phenyl ester.

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13. A method according to Claim 9 wherein the compound administered is sulfamic acid, [[2,4,6-tris(1-methylethyl)phenyl]acetyl]-2,6-bis(1-methylethyl)phenyl ester.
14. A method according to Claim 9 of inhibiting expression of matrix metalloproteinases in atherosclerotic lesions in a mammal, including the human, in need thereof comprising administering to said mammal an effective amount of a compound of Formula II above.
15. A method according to Claim 9 wherein the compound administered is selected from
- (±) 2-dodecyl- α -phenyl-N-(2,4,6-trimethoxyphenyl)-2H-tetrazole-5-acetamide,
- (±) 2-dodecyl-N, α -diphenyl-2H-tetrazole-5-acetamide,
- (±)-N-[2,6-bis(1-methylethyl)phenyl]-2-dodecyl- α -phenyl-2H-tetrazole-5-acetamide,
- (±)-N-(2,4-difluorophenyl)-2-dodecyl- α -phenyl-2H-tetrazole-5-acetamide,
- (±)-2-octyl- α -phenyl-N-(2,4,6-trimethoxyphenyl)-2H-tetrazole-5-acetamide, or
- (±)-2-hexadecyl- α -phenyl-N-(2,4,6-trimethoxyphenyl)-2H-tetrazole-5-acetamide.
16. A method according to Claim 9 wherein the compound administered is selected from
- (±)-N-[2,6-Bis(1-methylethyl)phenyl]-2-(2-dodecyl-2H-tetrazol-5-yl)-2-phenyl-acetamide,
- (+)-N-[2,6-Bis(1-methylethyl)phenyl]-2-(2-dodecyl-2H-tetrazol-5-yl)-2-phenyl-acetamide, or
- (-)-N-[2,6-Bis(1-methylethyl)phenyl]-2-(2-dodecyl-2H-tetrazol-5-yl)-2-phenyl-acetamide.

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17. A method of inhibiting the destabilization of atherosclerotic lesions in a mammal, including the human, in need of such treatment comprising administering to said mammal a therapeutically effective amount of any ACAT inhibitor.
- 5 18. A method according to Claim 17 of inhibiting the destabilization of atherosclerotic lesions in a mammal, including the human, in need thereof comprising administering to said mammal a therapeutically effective amount of a compound of Formula I above.
- 10 19. A method according to Claim 17 wherein R₁ and R₂ are independently selected from substituted phenyl or



15

wherein t and w are independently an integer of from 0 to 4 with the proviso that the sum of t and w is not greater than 5; R₅ and R₆ are each independently selected from hydrogen or alkyl having from 1 to 6 carbon atoms, or when R₅ is hydrogen, R₆ can be selected from the groups

20 defined for R₇; and R₇ is phenyl or phenyl substituted with from 1 to 3 substituents selected from a straight or branched alkyl group having from 1 to 6 carbon atoms, straight or branched alkoxy group having from 1 to 6 carbon atoms, phenoxy, hydroxy, fluorine, chlorine, bromine, nitro, trifluoromethyl, -COOH, -COOalkyl, wherein alkyl has from 1 to 4 carbon

25 atoms, or -(CH₂)_pNR₃R₄;

X is oxygen;

Y is (CR'R'')_n; and

R is hydrogen

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wherein n is an integer of 1 or 2, and substituted phenyl, p, R₃, R₄, R', and R'' have the meanings as defined above.

20. A method according to Claim 17 wherein the compound administered is selected from
 - 5 Sulfamic acid (phenylacetyl)-2,6-bis(1-methylethyl)phenyl ester,
Sulfamic acid[[2,6-bis(1-methylethyl)phenyl]acetyl]-
2,6-bis(1-methylethyl)phenyl ester,
Sulfamic acid [[2,4,6-tris(1-methylethyl)phenyl]acetyl]-
2,4,6-tris(1-methylethyl)phenyl ester,
 - 10 Sulfamic acid[[2,6-bis(1-methylethyl)phenyl]acetyl]-
2,4,6-tris(1-methylethyl)phenyl ester,
Sulfamic acid[adamantaneacetyl]-2,6-bis(1-methylethyl)phenyl
ester,
Sulfamic acid[[2,6-bis(1-methylethyl)phenyl]acetyl]-
15 2,6-bis(1-methylethyl)phenyl ester-sodium salt,
Sulfamic acid[[2,4,6-tris(1-methylethyl)phenyl]acetyl]-
2,6-bis(1-methylethyl)phenyl ester-sodium salt,
Sulfamic acid (decanoyl)-2,6-bis-(1-methylethyl)phenyl ester,
Sulfamic acid (dodecanoyl)-2,6-bis-(1-methylethyl)phenyl ester,
 - 20 2,6-Bis(1-methylethyl)-N-[[[2,4,6-tris(1-methylethyl)phenyl]-
methyl]sulfonyl]benzeneacetamide,
2,6-Bis(1-methylethyl)-N-[[[2,4,6-tris(1-methylethyl)phenyl]-
methyl]sulfonyl]benzeneacetamide-sodium salt,
2,6-Bis(1-methylethyl)phenyl[[[2,4,6-tris(1-methylethyl)phenyl]-
25 methyl]sulfonyl]carbamate,
2,6-Bis(1-methylethyl)phenyl[[[2,4,6-tris(1-methylethyl)phenyl]-
methyl]sulfonyl]carbamate-sodium salt,
Sulfamic acid (1-oxo-3,3-diphenylpropyl)-2,6-bis(1-
methylethyl)phenyl ester,
 - 30 Sulfamic acid [2,6-dichlorophenyl(acetyl)]-2,6-bis(1-
methylethyl)phenyl ester,

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Sulfamic acid [2,6-dichlorophenyl(acetyl)]-2,6-bis(1-methylethyl)phenyl ester,

Sulfamic acid trans-[(2-phenylcyclopropyl)carbonyl]-2,6-bis(1-methylethyl)phenyl ester,

5 Sulfamic acid [2,5-dimethoxyphenyl(acetyl)]-2,6-bis(1-methylethyl)phenyl ester,

Sulfamic acid [2,4,6-trimethoxyphenyl(acetyl)]-2,6-bis(1-methylethyl)phenyl ester,

10 Sulfamic acid [2,4,6-trimethylphenyl(acetyl)]-2,6-bis(1-methylethyl)phenyl ester,

Sulfamic acid [2-thiophenyl(acetyl)]-2,6-bis(1-methylethyl)phenyl ester,

Sulfamic acid [3-thiophenyl(acetyl)]-2,6-bis(1-methylethyl)phenyl ester,

15 Sulfamic acid [2-methoxyphenyl(acetyl)]-2,6-bis(1-methylethyl)phenyl ester,

Sulfamic acid (oxophenylacetyl)-2,6-bis(1-methylethyl)phenyl ester,

20 Sulfamic acid [2-trifluoromethylphenyl(acetyl)]-2,6-bis(1-methylethyl)phenyl ester,

Sulfamic acid (1-oxo-2-phenylpropyl)-2,6-bis(1-methylethyl)phenyl ester,

Sulfamic acid (cyclopentylphenylacetyl)-2,6-bis(1-methylethyl)phenyl ester,

25 Sulfamic acid (cyclohexylacetyl)-2,6-bis(1-methylethyl)phenyl ester,

Sulfamic acid (diphenylacetyl)-2,6-bis(1-methylethyl)phenyl ester,

Sulfamic acid (triphenylacetyl)-2,6-bis(1-methylethyl)phenyl ester,

30 Sulfamic acid [(1-phenylcyclopentyl)carbonyl]-2,6-bis(1-methylethyl)phenyl ester,

Sulfamic acid (3-methyl-1-oxo-2-phenylpentyl)-2,6-bis(1-methylethyl)phenyl ester,

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Sulfamic acid (1-oxo-2-phenylbutyl)-2,6-bis(1-methylethyl)phenyl ester,

Sulfamic acid (cyclohexylphenylacetyl)-2,6-bis(1-methylethyl)phenyl ester,

5 Sulfamic acid (1-oxo-2,2-diphenylpropyl)-2,6-bis(1-methylethyl)phenyl ester,

Sulfamic acid [(9H-fluoren-9-yl)carbonyl]-2,6-bis(1-methylethyl)phenyl ester,

10 Sulfamic acid (1-oxo-3-phenylpropyl)-2,6-bis(1-methylethyl)phenyl ester,

Sulfamic acid [1-oxo-3-[2,4,6-tris(1-methylethyl)phenyl]-2-propenyl]-2,6-bis(1-methylethyl)phenyl ester,

Sulfamic acid [1-oxo-3-[2,4,6-tris(1-methylethyl)phenyl]propyl]-2,6-bis(1-methylethyl)phenyl ester,

15 Sulfamic acid [(acetyloxy)[2,4,6-tris(1-methylethyl)phenyl]acetyl]-2,6-bis(1-methylethyl)phenyl ester,

Sulfamic acid [hydroxy[2,4,6-tris(1-methylethyl)phenyl]acetyl]-2,6-bis(1-methylethyl)phenyl ester,

20 Sulfamic acid [fluoro[2,4,6-tris(1-methylethyl)phenyl]acetyl]-2,6-bis(1-methylethyl)phenyl ester,

Sulfamic acid (3-methyl-1-oxo-2-phenylpentyl)-2,6-bis(1-methylethyl)phenyl ester sodium salt,

Sulfamic acid [[2,4,6-tris(1-methylethyl)phenoxy]acetyl]-2,6-bis(1-methylethyl)phenyl ester,

25 Sulfamic acid [[2,6-bis(1-methylethyl)phenoxy]acetyl]-2,6-bis(1-methylethyl)phenyl ester, and

Sulfamic acid [[2,4,6-tris(1-methylethyl)phenyl]acetyl]-2,6-bis(phenyl)phenyl ester.

21. A method according to Claim 17 wherein the compound administered is
30 Sulfamic acid, [[2,4,6-tris(1-methylethyl)phenyl]acetyl]-2,6-bis(1-methylethyl)phenyl ester.

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22. A method according to Claim 17 of inhibiting the destabilization of atherosclerotic lesions in a mammal, including the human, in need thereof comprising administering to said mammal a therapeutically effective amount of a compound of Formula II above.
- 5 23. A method according to Claim 17 wherein the compound administered is selected from
- (±) 2-dodecyl- α -phenyl-N-(2,4,6-trimethoxyphenyl)-2H-tetrazole-5-acetamide,
- (±) 2-dodecyl-N, α -diphenyl-2H-tetrazole-5-acetamide,
- 10 (±)-N-[2,6-bis(1-methylethyl)phenyl]-2-dodecyl- α -phenyl-2H-tetrazole-5-acetamide,
- (±)-N-(2,4-difluorophenyl)-2-dodecyl- α -phenyl-2H-tetrazole-5-acetamide,
- (±)-2-octyl- α -phenyl-N-(2,4,6-trimethoxyphenyl)-2H-tetrazole-5-acetamide, or
- 15 (±)-2-hexadecyl- α -phenyl-N-(2,4,6-trimethoxyphenyl)-2H-tetrazole-5-acetamide.
24. A method according to Claim 17 wherein the compound administered is selected from
- 20 (±)-N-[2,6-Bis(1-methylethyl)phenyl]-2-(2-dodecyl-2H-tetrazol-5-yl)-2-phenyl-acetamide,
- (+)-N-[2,6-Bis(1-methylethyl)phenyl]-2-(2-dodecyl-2H-tetrazol-5-yl)-2-phenyl-acetamide, or
- (-)-N-[2,6-Bis(1-methylethyl)phenyl]-2-(2-dodecyl-2H-tetrazol-5-yl)-2-phenyl-acetamide.
- 25 25. A method of preventing atherosclerotic plaque rupture in a mammal, including the human, in need of such treatment comprising administering to said mammal a therapeutically effective amount of any ACAT inhibitor.

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26. A method according to Claim 25 of preventing atherosclerotic plaque rupture in a mammal, including the human, in need thereof comprising administering to said mammal a therapeutically effective amount of a compound of Formula I above.

5 27. A method according to Claim 25 wherein
 R_1 and R_2 are independently selected from substituted phenyl or



15 wherein t and w are independently an integer of from 0 to 4 with the proviso that the sum of t and w is not greater than 5; R_5 and R_6 are each independently selected from hydrogen or alkyl having from 1 to 6 carbon atoms, or when R_5 is hydrogen, R_6 can be selected from the groups
 20 defined for R_7 ; and R_7 is phenyl or phenyl substituted with from 1 to 3 substituents selected from a straight or branched alkyl group having from 1 to 6 carbon atoms, straight or branched alkoxy group having from 1 to 6 carbon atoms, phenoxy, hydroxy, fluorine, chlorine, bromine, nitro, trifluoromethyl, $-COOH$, $-COO$ alkyl, wherein alkyl has from 1 to 4 carbon atoms, or $-(CH_2)_pNR_3R_4$;

X is oxygen;

Y is $(CR'R'')_n$; and

R is hydrogen

25 wherein n is an integer of 1 or 2, and substituted phenyl, p, R_3 , R_4 , R' , and R'' have the meanings as defined above.

28. A method according to Claim 25 wherein the compound administered is selected from

Sulfamic acid (phenylacetyl)-2,6-bis(1-methylethyl)phenyl ester,

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Sulfamic acid[[2,6-bis(1-methylethyl)phenyl]acetyl]-2,6-bis(1-methylethyl)phenyl ester,

Sulfamic acid [[2,4,6-tris(1-methylethyl)phenyl]acetyl]-2,4,6-tris(1-methylethyl)phenyl ester,

5 Sulfamic acid[[2,6-bis(1-methylethyl)phenyl]acetyl]-2,4,6-tris(1-methylethyl)phenyl ester,

Sulfamic acid[adamantaneacetyl]-2,6-bis(1-methylethyl)phenyl ester,

10 Sulfamic acid[[2,6-bis(1-methylethyl)phenyl]acetyl]-2,6-bis(1-methylethyl)phenyl ester-sodium salt,

Sulfamic acid[[2,4,6-tris(1-methylethyl)phenyl]acetyl]-2,6-bis(1-methylethyl)phenyl ester-sodium salt,

Sulfamic acid (decanoyl)-2,6-bis-(1-methylethyl)phenyl ester,

15 Sulfamic acid (dodecanoyl)-2,6-bis-(1-methylethyl)phenyl ester,
2,6-Bis(1-methylethyl)-N-[[[2,4,6-tris(1-methylethyl)phenyl]-methyl]sulfonyl]benzeneacetamide,

2,6-Bis(1-methylethyl)-N-[[[2,4,6-tris(1-methylethyl)phenyl]-methyl]sulfonyl]benzeneacetamide-sodium salt,

20 2,6-Bis(1-methylethyl)phenyl[[[2,4,6-tris(1-methylethyl)phenyl]-methyl]sulfonyl]carbamate,

2,6-Bis(1-methylethyl)phenyl[[[2,4,6-tris(1-methylethyl)phenyl]-methyl]sulfonyl]carbamate-sodium salt,

Sulfamic acid (1-oxo-3,3-diphenylpropyl)-2,6-bis(1-methylethyl)phenyl ester,

25 Sulfamic acid [2,6-dichlorophenyl(acetyl)]-2,6-bis(1-methylethyl)phenyl ester,

Sulfamic acid [2,6-dichlorophenyl(acetyl)]-2,6-bis(1-methylethyl)phenyl ester,

30 Sulfamic acid trans-[(2-phenylcyclopropyl)carbonyl]-2,6-bis(1-methylethyl)phenyl ester,

Sulfamic acid [2,5-dimethoxyphenyl(acetyl)]-2,6-bis(1-methylethyl)phenyl ester,

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Sulfamic acid [2,4,6-trimethoxyphenyl(acetyl)]-2,6-bis(1-methylethyl)phenyl ester,

Sulfamic acid [2,4,6-trimethylphenyl(acetyl)]-2,6-bis(1-methylethyl)phenyl ester,

5 Sulfamic acid [2-thiophenyl(acetyl)]-2,6-bis(1-methylethyl)phenyl ester,

Sulfamic acid [3-thiophenyl(acetyl)]-2,6-bis(1-methylethyl)phenyl ester,

10 Sulfamic acid [2-methoxyphenyl(acetyl)]-2,6-bis(1-methylethyl)phenyl ester,

Sulfamic acid (oxophenylacetyl)-2,6-bis(1-methylethyl)phenyl ester,

Sulfamic acid [2-trifluoromethylphenyl(acetyl)]-2,6-bis(1-methylethyl)phenyl ester,

15 Sulfamic acid (1-oxo-2-phenylpropyl)-2,6-bis(1-methylethyl)phenyl ester,

Sulfamic acid (cyclopentylphenylacetyl)-2,6-bis(1-methylethyl)phenyl ester,

20 Sulfamic acid (cyclohexylacetyl)-2,6-bis(1-methylethyl)phenyl ester,

Sulfamic acid (diphenylacetyl)-2,6-bis(1-methylethyl)phenyl ester,

Sulfamic acid (triphenylacetyl)-2,6-bis(1-methylethyl)phenyl ester,

Sulfamic acid [(1-phenylcyclopentyl)carbonyl]-2,6-bis(1-methylethyl)phenyl ester,

25 Sulfamic acid (3-methyl-1-oxo-2-phenylpentyl)-2,6-bis(1-methylethyl)phenyl ester,

Sulfamic acid (1-oxo-2-phenylbutyl)-2,6-bis(1-methylethyl)phenyl ester,

30 Sulfamic acid (cyclohexylphenylacetyl)-2,6-bis(1-methylethyl)phenyl ester,

Sulfamic acid (1-oxo-2,2-diphenylpropyl)-2,6-bis(1-methylethyl)phenyl ester,

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Sulfamic acid [(9H-fluoren-9-yl)carbonyl]-2,6-bis(1-methylethyl)phenyl ester,

Sulfamic acid (1-oxo-3-phenylpropyl)-2,6-bis(1-methylethyl)phenyl ester,

5 Sulfamic acid [1-oxo-3-[2,4,6-tris(1-methylethyl)phenyl]-2-propenyl]-2,6-bis(1-methylethyl)phenyl ester,

Sulfamic acid [1-oxo-3-[2,4,6-tris(1-methylethyl)phenyl]propyl]-2,6-bis(1-methylethyl)phenyl ester,

10 Sulfamic acid [(acetyloxy)[2,4,6-tris(1-methylethyl)phenyl]acetyl]-2,6-bis(1-methylethyl)phenyl ester,

Sulfamic acid [hydroxy[2,4,6-tris(1-methylethyl)phenyl]acetyl]-2,6-bis(1-methylethyl)phenyl ester,

Sulfamic acid [fluoro[2,4,6-tris(1-methylethyl)phenyl]acetyl]-2,6-bis(1-methylethyl)phenyl ester,

15 Sulfamic acid (3-methyl-1-oxo-2-phenylpentyl)-2,6-bis(1-methylethyl)phenyl ester sodium salt,

Sulfamic acid [[2,4,6-tris(1-methylethyl)phenoxy]acetyl]-2,6-bis(1-methylethyl)phenyl ester,

20 Sulfamic acid [[2,6-bis(1-methylethyl)phenoxy]acetyl]-2,6-bis(1-methylethyl)phenyl ester, and

Sulfamic acid [[2,4,6-tris(1-methylethyl)phenyl]acetyl]-2,6-bis(phenyl)phenyl ester.

29. A method according to Claim 25 wherein the compound administered is
25 Sulfamic acid, [[2,4,6-tris(1-methylethyl)phenyl]acetyl]-2,6-bis(1-methylethyl)phenyl ester.

30. A method according to Claim 25 of preventing atherosclerotic plaque rupture in a mammal, including the human, in need thereof comprising administering to said mammal a therapeutically effective amount of a compound of Formula II above.

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31. A method according to Claim 25 wherein the compound administered is selected from
- (±) 2-dodecyl- α -phenyl-N-(2,4,6-trimethoxyphenyl)-2H-tetrazole-5-acetamide,
- 5 (±) 2-dodecyl-N, α -diphenyl-2H-tetrazole-5-acetamide,
- (±)-N-[2,6-bis(1-methylethyl)phenyl]-2-dodecyl- α -phenyl-2H-tetrazole-5-acetamide,
- (±)-N-(2,4-difluorophenyl)-2-dodecyl- α -phenyl-2H-tetrazole-5-acetamide,
- 10 (±)-2-octyl- α -phenyl-N-(2,4,6-trimethoxyphenyl)-2H-tetrazole-5-acetamide, or
- (±)-2-hexadecyl- α -phenyl-N-(2,4,6-trimethoxyphenyl)-2H-tetrazole-5-acetamide.
32. A method according to Claim 25 wherein the compound administered is selected from
- 15 (±)-N-[2,6-Bis(1-methylethyl)phenyl]-2-(2-dodecyl-2H-tetrazol-5-yl)-2-phenyl-acetamide,
- (+)-N-[2,6-Bis(1-methylethyl)phenyl]-2-(2-dodecyl-2H-tetrazol-5-yl)-2-phenyl-acetamide, or
- 20 (-)-N-[2,6-Bis(1-methylethyl)phenyl]-2-(2-dodecyl-2H-tetrazol-5-yl)-2-phenyl-acetamide.
33. A method of treating unstable angina in a mammal, including the human, in need of such treatment comprising administering to said mammal a therapeutically effective amount of an ACAT inhibitor effective for
- 25 treating unstable angina.
34. A method according to Claim 33 of treating unstable angina in a mammal, including the human, in need thereof comprising administering to said mammal a therapeutically effective amount of a compound of Formula I above.

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35. A method according to Claim 33 wherein
 R_1 and R_2 are independently selected from substituted phenyl or



wherein t and w are independently an integer of from 0 to 4 with the proviso that the sum of t and w is not greater than 5; R_5 and R_6 are each independently selected from hydrogen or alkyl having from 1 to 6 carbon atoms, or when R_5 is hydrogen, R_6 can be selected from the groups defined for R_7 ; and R_7 is phenyl or phenyl substituted with from 1 to 3 substituents selected from a straight or branched alkyl group having from 1 to 6 carbon atoms, straight or branched alkoxy group having from 1 to 6 carbon atoms, phenoxy, hydroxy, fluorine, chlorine, bromine, nitro, trifluoromethyl, $-COOH$, $-COOalkyl$, wherein alkyl has from 1 to 4 carbon atoms, or $-(CH_2)_pNR_3R_4$;

X is oxygen;

Y is $(CR'R'')_n$; and

R is hydrogen

wherein n is an integer of 1 or 2, and substituted phenyl, p, R_3 , R_4 , R' , and R'' have the meanings as defined above.

36. A method according to Claim 33 wherein the compound administered is selected from
- Sulfamic acid (phenylacetyl)-2,6-bis(1-methylethyl)phenyl ester,
 Sulfamic acid[[2,6-bis(1-methylethyl)phenyl]acetyl]-
 2,6-bis(1-methylethyl)phenyl ester,
 Sulfamic acid [[2,4,6-tris(1-methylethyl)phenyl]acetyl]-
 2,4,6-tris(1-methylethyl)phenyl ester,

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Sulfamic acid[[2,6-bis(1-methylethyl)phenyl]acetyl]-
2,4,6-tris(1-methylethyl)phenyl ester,

Sulfamic acid[adamantaneacetyl]-2,6-bis(1-methylethyl)phenyl
ester,

5 Sulfamic acid[[2,6-bis(1-methylethyl)phenyl]acetyl]-
2,6-bis(1-methylethyl)phenyl ester-sodium salt,

Sulfamic acid[[2,4,6-tris(1-methylethyl)phenyl]acetyl]-
2,6-bis(1-methylethyl)phenyl ester-sodium salt,

10 Sulfamic acid (decanoyl)-2,6-bis-(1-methylethyl)phenyl ester,
Sulfamic acid (dodecanoyl)-2,6-bis-(1-methylethyl)phenyl ester,
2,6-Bis(1-methylethyl)-N-[[[2,4,6-tris(1-methylethyl)phenyl]-
methyl]sulfonyl]benzeneacetamide,

2,6-Bis(1-methylethyl)-N-[[[2,4,6-tris(1-methylethyl)phenyl]-
methyl]sulfonyl]benzeneacetamide-sodium salt,

15 2,6-Bis(1-methylethyl)phenyl[[[2,4,6-tris(1-methylethyl)phenyl]-
methyl]sulfonyl]carbamate,

2,6-Bis(1-methylethyl)phenyl[[[2,4,6-tris(1-methylethyl)phenyl]-
methyl]sulfonyl]carbamate-sodium salt,

20 Sulfamic acid (1-oxo-3,3-diphenylpropyl)-2,6-bis(1-
methylethyl)phenyl ester,

Sulfamic acid [2,6-dichlorophenyl(acetyl)]-2,6-bis(1-
methylethyl)phenyl ester,

Sulfamic acid [2,6-dichlorophenyl(acetyl)]-2,6-bis(1-
methylethyl)phenyl ester,

25 Sulfamic acid trans-[(2-phenylcyclopropyl)carbonyl]-2,6-bis(1-
ethylethyl)phenyl ester,

Sulfamic acid [2,5-dimethoxyphenyl(acetyl)]-2,6-bis(1-
methylethyl)phenyl ester,

30 Sulfamic acid [2,4,6-trimethoxyphenyl(acetyl)]-2,6-bis(1-
methylethyl)phenyl ester,

Sulfamic acid [2,4,6-trimethylphenyl(acetyl)]-2,6-bis(1-
methylethyl)phenyl ester,

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Sulfamic acid [2-thiophenyl(acetyl)]-2,6-bis(1-methylethyl)phenyl ester,

Sulfamic acid [3-thiophenyl(acetyl)]-2,6-bis(1-methylethyl)phenyl ester,

5 Sulfamic acid [2-methoxyphenyl(acetyl)]-2,6-bis(1-methylethyl)phenyl ester,

Sulfamic acid (oxophenylacetyl)-2,6-bis(1-methylethyl)phenyl ester,

10 Sulfamic acid [2-trifluoromethylphenyl(acetyl)]-2,6-bis(1-methylethyl)phenyl ester,

Sulfamic acid (1-oxo-2-phenylpropyl)-2,6-bis(1-methylethyl)phenyl ester,

Sulfamic acid (cyclopentylphenylacetyl)-2,6-bis(1-methylethyl)phenyl ester,

15 Sulfamic acid (cyclohexylacetyl)-2,6-bis(1-methylethyl)phenyl ester,

Sulfamic acid (diphenylacetyl)-2,6-bis(1-methylethyl)phenyl ester,

Sulfamic acid (triphenylacetyl)-2,6-bis(1-methylethyl)phenyl ester,

20 Sulfamic acid [(1-phenylcyclopentyl)carbonyl]-2,6-bis(1-methylethyl)phenyl ester,

Sulfamic acid (3-methyl-1-oxo-2-phenylpentyl)-2,6-bis(1-methylethyl)phenyl ester,

Sulfamic acid (1-oxo-2-phenylbutyl)-2,6-bis(1-methylethyl)phenyl ester,

25 Sulfamic acid (cyclohexylphenylacetyl)-2,6-bis(1-methylethyl)phenyl ester,

Sulfamic acid (1-oxo-2,2-diphenylpropyl)-2,6-bis(1-methylethyl)phenyl ester,

30 Sulfamic acid [(9H-fluoren-9-yl)carbonyl]-2,6-bis(1-methylethyl)phenyl ester,

Sulfamic acid (1-oxo-3-phenylpropyl)-2,6-bis(1-methylethyl)phenyl ester,

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Sulfamic acid [1-oxo-3-[2,4,6-tris(1-methylethyl)phenyl]-2-propenyl]-2,6-bis(1-methylethyl)phenyl ester,

Sulfamic acid [1-oxo-3-[2,4,6-tris(1-methylethyl)phenyl]propyl]-2,6-bis(1-methylethyl)phenyl ester,

5 Sulfamic acid [(acetyloxy)[2,4,6-tris(1-methylethyl)phenyl]acetyl]-2,6-bis(1-methylethyl)phenyl ester,

Sulfamic acid [hydroxy[2,4,6-tris(1-methylethyl)phenyl]acetyl]-2,6-bis(1-methylethyl)phenyl ester,

10 Sulfamic acid [fluoro[2,4,6-tris(1-methylethyl)phenyl]acetyl]-2,6-bis(1-methylethyl)phenyl ester,

Sulfamic acid (3-methyl-1-oxo-2-phenylpentyl)-2,6-bis(1-methylethyl)phenyl ester sodium salt,

Sulfamic acid [[2,4,6-tris(1-methylethyl)phenoxy]acetyl]-2,6-bis(1-methylethyl)phenyl ester,

15 Sulfamic acid [[2,6-bis(1-methylethyl)phenoxy]acetyl]-2,6-bis(1-methylethyl)phenyl ester, and

Sulfamic acid [[2,4,6-tris(1-methylethyl)phenyl]acetyl]-2,6-bis(phenyl)phenyl ester.

20 37. A method according to Claim 33 wherein the compound administered is Sulfamic acid, [[2,4,6-tris(1-methylethyl)phenyl]acetyl]-2,6-bis(1-methylethyl)phenyl ester.

25 38. A method according to Claim 33 of treating unstable angina in a mammal, including the human, in need thereof comprising administering to said mammal a therapeutically effective amount of a compound of Formula II above.

39. A method according to Claim 33 wherein the compound administered is selected from
(±) 2-dodecyl- α -phenyl-N-(2,4,6-trimethoxyphenyl)-2H-tetrazole-5-acetamide,
30 (±) 2-dodecyl-N, α -diphenyl-2H-tetrazole-5-acetamide,

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(±)-N-[2,6-bis(1-methylethyl)phenyl]-2-dodecyl- α -phenyl-2H-tetrazole-5-acetamide,

(±)-N-(2,4-difluorophenyl)-2-dodecyl- α -phenyl-2H-tetrazole-5-acetamide,

5 (±)-2-octyl- α -phenyl-N-(2,4,6-trimethoxyphenyl)-2H-tetrazole-5-acetamide, or

(±)-2-hexadecyl- α -phenyl-N-(2,4,6-trimethoxyphenyl)-2H-tetrazole-5-acetamide.

40. A method according to Claim 33 wherein the compound administered is
10 selected from

(±)-N-[2,6-Bis(1-methylethyl)phenyl]-2-(2-dodecyl-2H-tetrazol-5-yl)-2-phenyl-acetamide,

(+)-N-[2,6-Bis(1-methylethyl)phenyl]-2-(2-dodecyl-2H-tetrazol-5-yl)-2-phenyl-acetamide, or

15 (-)-N-[2,6-Bis(1-methylethyl)phenyl]-2-(2-dodecyl-2H-tetrazol-5-yl)-2-phenyl-acetamide.

41. A method according to Claim 1 wherein the compound administered is selected from:

20 N-[2,6-Bis(1-methylethyl)phenyl]-2-dodecyl-2H-tetrazole-5-acetamide;

2-Dodecyl-N-(2,4,6-trimethoxyphenyl)-2H-tetrazole-5-acetamide;

N-(2,4-Difluorophenyl)-2-dodecyl-2H-tetrazole-5-acetamide;

2-Tetradecyl-N-(2,4,6-tri-methoxyphenyl)-2H-tetrazole-5-acetamide;

25 N-(4,6-Dimethoxy-5-pyrimidinyl)-2-dodecyl-2H-tetrazole-5-acetamide;

N-(4,6-Dimethoxy-5-pyrimidinyl)-2-dodecyl-1H-tetrazole-5-acetamide;

2-Dodecyl-N-(3-methyl-2-pyridinyl)-2H-tetrazole-5-acetamide;

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2-Dodecyl-N-(1,3,5-trimethyl-1H-pyrazol-4-yl)-2H-tetrazole-5-acetamide;

1-Dodecyl-N-(1,3,5-trimethyl-1H-pyrazol-4-yl)-1H-tetrazole-5-acetamide;

5 (±) 2-Dodecyl- α -phenyl-N-(2,4,6-trimethoxyphenyl)-2H-tetrazole-5-acetamide;

(±) 2-Dodecyl-N, α -diphenyl-2H-tetrazole-5-acetamide;

(±)-N-[2,6-bis(1-Methylethyl)phenyl]-2-dodecyl- α -phenyl-2H-tetrazole-5-acetamide;

10 (±)-N-(2,4-Difluorophenyl)-2-dodecyl- α -phenyl-2H-tetrazole-5-acetamide;

(±)-2-Octyl- α -phenyl-N-(2,4,6-trimethoxyphenyl)-2H-tetrazole-5-acetamide;

15 (±)-2-Hexadecyl- α -phenyl-N-(2,4,6-trimethoxyphenyl)-2H-tetrazole-5-acetamide;

(±)-N-(4,6-Dimethoxy-5-pyrimidinyl)-2-dodecyl- α -phenyl-2H-tetrazole-5-acetamide;

(±)-N-(5,7-Dimethyl-1,8-naphthyridine-2-yl)-2-dodecyl- α -phenyl-2H-tetrazole-5-acetamide;

20 (±)-2-Dodecyl- α -phenyl-N-(1,3,5-trimethyl-1H-pyrazol-4-yl)-2H-tetrazole-5-acetamide;

(±)-N-Cyclopropyl-2-dodecyl- α -phenyl-2H-tetrazole-5-acetamide;

(±)-2-Dodecyl- α -phenyl-N-2-pyridinyl-2H-tetrazole-5-acetamide;

25 (±)-2-Dodecyl-N-(3-methyl-2-pyridinyl)- α -phenyl-2H-tetrazole-5-acetamide;

(±)-2-Dodecyl-N-(3-methyl-2-pyridinyl)-2-phenyl-2H-tetrazole-5-acetamide, N-oxide;

(±)-N-(1,1-Dimethylethyl)-2-dodecyl- α -phenyl-2H-tetrazole-5-acetamide;

30 (±)-2-Dodecyl- α -(2-pyridyl)-N-(2,4,6-trimethoxyphenyl)-2H-tetrazole-5-acetamide;

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(±)-N-[2,6-Bis(1-methylethyl)phenyl]-2-dodecyl-α-2-pyridinyl-
2H-tetrazole-5-acetamide;

2-Dodecyl-α,α-dimethyl-N-(2,4,6-trimethoxyphenyl)-2H-tetrazole-
5-acetamide;

5 2-Dodecyl-α,α'-(2-propenyl)-N-(2,4,6-trimethoxyphenyl)-2H-
tetrazole-5-acetamide;

1-(2-Dodecyl-2H-tetrazol-5-yl)-N-(2,4,6-trimethoxyphenyl)-
cyclopentanecarboxamide;

10 2-Tridecyl-α,α-dimethyl-N-(2,4,6-trimethoxyphenyl)-2H-tetrazole-
5-acetamide;

2-Dodecyl-N-(2,4,6-trimethoxyphenyl)-2H-tetrazole-
5-propanamide;

N-(2,6-bis(1-Methylethyl)phenyl)-2-dodecyl-2H-tetrazole-
5-propanamide;

15 N-(2,4-Difluorophenyl)-2-dodecyl-2H-tetrazole-5-propanamide;

1-Dodecyl-N-(2,4,6-trimethoxyphenyl)-1H-tetrazole-
5-propanamide;

(±)-n-(2,4-Difluorophenyl)-1-dodecyl-α-phenyl-1H-tetrazole-
5-acetamide;

20 (±)-N-[2,6-bis(1-Methylethyl)phenyl]-1-dodecyl-α-phenyl-1H-
tetrazole-5-acetamide;

(±)-2-Dodecyl-α-methyl-α-phenyl-N-(2,4,6-trimethoxyphenyl)-
2H-tetrazole-5-acetamide;

25 (±)-2-Dodecyl-α-(4-fluorophenyl)-N-(2,4,6-trimethoxyphenyl)-2H-
tetrazole-5-acetamide;

(±)-2-Dodecyl-α-2-naphthalenyl-N-(2,4,6-trimethoxyphenyl)-2H-
tetrazole-5-acetamide;

(±)-α-([1,1'-Biphenyl]-4-yl)-2-dodecyl-N-(2,4,6-trimethoxy-
phenyl)-2H-tetrazole-5-acetamide;

30 (±)-2-Dodecyl-α-methyl-N-(2,4,6-trimethoxy-phenyl)-2H-
tetrazole-5-acetamide;

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(±)-2-Dodecyl- α -phenylmethyl-N-(2,4,6-trimethoxyphenyl)-2H-tetrazole-5-acetamide;

(±)-2-Dodecyl- α -cyclohexyl-N-(2,4,6-trimethoxy-phenyl)-2H-tetrazole-5-acetamide;

5 (-)-2-Dodecyl- α -phenyl-N-(2,4,6-trimethoxy-phenyl)-2H-tetrazole-5-acetamide $[\alpha]_D = -58^\circ$ (1% in CH₃OH);

(+)-2-Dodecyl- α -phenyl-N-(2,4,6-trimethoxy-phenyl)-2H-tetrazole-5-acetamide $[\alpha]_D = +55.1^\circ$ (1% in CH₃OH);

10 (±)-N-[2,6-Bis(1-Methylethyl)phenyl]-2-dodecyl- α -fluoro- α -phenyl-2H-tetrazole-5-acetamide;

(±)-2-Dodecyl- α -fluoro- α -phenyl-N-(2,4,6-trimethoxy phenyl)-2H-tetrazole-5-acetamide;

N-[2,6-bis(1-Methylethyl)phenyl]-5-decyl-2H-tetrazole-2-acetamide;

15 N-[2,6-bis(1-Methylethyl)phenyl]-5-dodecyl-2H-tetrazole-2-acetamide;

(±)-N-[2,6-bis(1-Methylethyl)phenyl]-5-dodecyl- α -phenyl-2H-tetrazole-2-acetamide;

20 (±)-N-[2,6-bis(1-Methylethyl)phenyl]-5-dodecyl- α -pentyl-2H-tetrazole-2-acetamide;

(±)-N-[2,6-bis(1-Methylethyl)phenyl]-5-(dodecylthio)- α -phenyl-2H-tetrazole-2-acetamide;

(±)-5-Decyl- α -phenyl-N-(2,4,6-trimethoxyphenyl)-2H-tetrazole-2-acetamide;

25 5-Dodecyl-N-(2,4,6-trimethoxy-phenyl)-2H-tetrazole-2-acetamide;

(±)-5-Dodecyl- α -phenyl-N-(2,4,6-trimethoxyphenyl)-2H-tetrazole-2-acetamide;

(±)-5-Dodecyl- α -pentyl-N-(2,4,6-trimethoxyphenyl)-2H-tetrazole-2-acetamide;

30 (±)-N-(2,4-Difluorophenyl)-5-dodecyl- α -phenyl-2H-tetrazole-2-acetamide;

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5-Dodecyl- α,α -dimethyl-N-(2,4,6-trimethoxyphenyl)-2H-tetrazole-2-acetamide;

(\pm)-5-(Dodecylthio)- α -phenyl-N-(2,4,6-trimethoxyphenyl)-2H-tetrazole-2-acetamide; or

5 (\pm)-5-(Dodecylsulfinyl)- α -phenyl-N-(2,4,6-trimethoxyphenyl)-2H-tetrazole-2-acetamide.

42. A method according to Claim 1 wherein the compound administered is selected from

- 4-Hexadecylamino-benzoic acid monosodium salt;
- 10 3,5-Dimethyl-1-[5-(1,4,5-triphenyl-2H-imidazol-2-ylsulfanyl)-pentyl]-1H-pyrazole monosodium salt;
- 8-(1,4,5-Triphenyl-2H-imidazol-2-yloxy)-octanoic acid;
- 9-Bromo-6,11-dihydro-dibenzo[b,e]oxepine-11-carboxylic acid (2,6-diisopropyl-phenyl)-amide;
- 15 5-((3,5-Di-tert-butyl-4-hydroxy-phenylamino)-{[4-(2,2-dimethyl-propyl)-benzyl]-hexyl-amino}-methylene)-2,2-dimethyl-[1,3]dioxane-4,6-di1;
- 3-(2,4-Difluoro-phenyl)-1-[4-(2,2-dimethyl-propyl)-benzyl]-1-heptyl-urea;
- 20 1-Heptyl-1-[4-(3-methyl-butyl)-benzyl]-3-(2,4,6-trifluoro-phenyl)-urea;
- 3-(2,4-Difluoro-phenyl)-1-[5-(4,5-diphenyl-1H-imidazol-2-ylsulfanyl)-pentyl]-1-heptyl-urea;
- 1-Butyl-3-{2-[3-(5-ethyl-4-phenyl-imidazol-1-yl)-propoxy]-6-methyl-phenyl}-urea;
- 25 1-(2-{2-[4-(2,2-Dimethyl-propyl)-phenyl]-ethyl}-4,6-difluoro-phenyl)-3-heptyl-urea;
- Octadeca-9,12-dienoic acid (1-phenyl-ethyl)-amide;
- 3-(1H-Indol-3-yl)-2-octadec-9-enoylamino-propionic acid ethyl
- 30 ester;

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3-(Dimethyl-nonyl-silanyl)-N-(1-phenyl-2-p-tolyl-ethyl)-
propionamide;

(R)2-Hexyl-decanoic acid (6-methyl-2,4-bis-methylsulfanyl-
pyridin-3-yl)-amide;

5 N-[2-(3,5-Di-tert-butyl-4-hydroxy-phenyl)-ethyl]-4-fluoro-
benzenesulfonamide;

2-(2-Ethoxy-ethylsulfanyl)-4,5-diphenyl-1H-imidazole;

4-Cyano-N-[2-(4-cyano-phenyl)-3-methyl-5,5-bis-trifluoromethyl-
4,5-dihydro-3H-imidazol-4-yl]-N-methyl-benzamide;

10 1-{3-[3-(1-Methyl-1H-imidazol-2-yl)-2-phenethyl-2H-chromen-
6-yloxy]-propyl}-cyclopentanecarboxylic acid ethyl ester;

1-[4-(2-Chloro-phenyl)-2-ethyl-thieno[2,3-b]pyridin-5-yl]-
3-(2,4-difluoro-phenyl)-urea;

15 1-(2-Cyclohexyl-[1,3]dithiolan-2-ylmethyl)-3-(2,6-diisopropyl-
phenyl)-urea;

1-Cycloheptyl-1-(2,3-dihydro-benzo[1,4]dioxin-5-ylmethyl)-
3-(2,4,6-trimethyl-phenyl)-urea;

1-{2-[4-(1,2-Dimethoxy-ethoxy)-phenyl]-ethyl}-3-(2,4-dimethoxy-
phenyl)-1-heptyl-urea;

20 2-(4-{2-[3-(2,4-Dimethoxy-phenyl)-1-heptyl-ureido]-ethyl}-
phenoxy)-2-methyl-propionic acid;

3-(2,4-Difluoro-phenyl)-1-octyl-1-(2,3,4,5-tetrahydro-
benzo[b]oxepin-5-yl)-urea;

N-(2,6-Diisopropyl-phenyl)-2-octadecylsulfanyl-acetamide;

25 2-Bromo-6,11-dihydro-dibenzo[b,e]oxepine-11-carboxylic acid
(2,6-diisopropyl-phenyl)-amide;

(±)N-(1,2-Diphenyl-ethyl)-3-(2-heptyloxy-phenyl)-propionamide;

2,2-Dimethyl-dodecanoic acid (7-methoxy-4-oxo-chroman-8-yl)-
amide;

30 (Z)1-(6,7-Dimethoxy-3,4-dihydro-1H-isoquinolin-2-yl)-octadec-
9-en-1-1;

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- (Z)2,2,5,5-Tetramethyl-[1,3]dioxane-4-carboxylic acid
[2-(2-octadec-9-enoylamino-ethylcarbamoyl)-ethyl]-amide;
1-Benzyl-1-(5-methyl-3-phenyl-benzofuran-2-ylmethyl)-
3-(2,4,6-trifluoro-phenyl)-urea;
- 5 5-Chloro-3-o-tolyl-benzofuran-2-carboxylic acid (2,6-diisopropyl-phenyl)-amide;
2-(2,4a-Dimethyl-4a,5-dihydro-naphthalen-1-ylsulfanyl)-N-
{2-[(6,6-dimethyl-hepta-2,4-diynyl)-pentyl-amino]-ethyl}-acetamide;
(Z)Octadec-9-enoic acid [2-(1,4-dioxa-8-aza-spiro[4.5]dec-8-yl)-
10 1-phenyl-ethyl]-amide;
N-(4-Dihexylamino-6-mercapto-2-methyl-pyrimidin-5-yl)-
4-(phenyl-propyl-amino)-butyramide;
(Z)1-(6,7-Dimethoxy-3-phenyl-3,4-dihydro-1H-isoquinolin-2-yl)-
octadec-9-en-1-1;
- 15 (trans)1,4-Bis-(4-methoxy-phenyl)-3-(3-phenyl-propyl)-azetidin-
2-1;
1-Butyl-3-{2-dimethylamino-6-[3-(4-phenyl-imidazol-1-yl)-
propoxy]-phenyl}-urea;
1-{2-Dimethylamino-6-[3-(4-phenyl-imidazol-1-yl)-propoxy]-
20 phenyl}-3-pentyl-urea;
1-{2-Dimethylamino-6-[3-(5-methyl-4-phenyl-imidazol-1-yl)-
propoxy]-phenyl}-3-pentyl-urea;
1-(2-{2-[4-(2,2-Dimethyl-propyl)-phenyl]-ethyl}-4,6-difluoro-
phenyl)-3-heptyl-urea;
- 25 (4S-trans)6-(4,5-Diphenyl-1H-imidazol-2-ylsulfanylmethyl)-
4-hydroxy-4-methyl-tetrahydro-pyran-2-1;
2-(3-[1,3]Dioxan-2-yl-propylsulfanyl)-4,5-diphenyl-1H-imidazole;
Hydroxy-phenyl-acetic acid 3,3,5-trimethyl-cyclohexyl ester;
Acetic acid 1-(11-hydroxy-4-methoxy-9-methyl-5-oxo-5H,7H-
30 6,12-dioxa-dibenzo[a,d]-cycloocten-3-yl)-3-methyl-butyl ester;
10-Hydroxy-2,4a,6a,6b,9,10,12a-heptamethyl-4-octadecanoyloxy-
1,2,3,4,4a,5,6, 6a,6b,7,8,8a,9,10, 11,12,12a,12b,13,14b-eicosahydro-
picene-2-carboxylic acid;

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3-[(2,2,5,5-Tetramethyl-[1,3]dioxane-4-carbonyl)-amino]-
propionic acid 2-[3-(2,2-dimethyl-propyl)-3-nonyl-ureido]-cyclohexyl
ester;

1-(2,6-Diisopropyl-phenyl)-3-(2-p-tolyl-heptyl)-urea;

5 1-[4-(2-Chloro-phenyl)-6,8-dimethyl-quinolin-3-yl]-3-(2,4-
difluoro-phenyl)-urea;

1-[4-(2-Chloro-phenyl)-1,6,7-trimethyl-2-oxo-1,2-dihydro-
quinolin-3-yl]-3-(2,4-difluoro-phenyl)-urea;

10 1-[4-(2-Chloro-phenyl)-6,7-dimethyl-2-oxo-2H-chromen-3-yl]-
3-(2,4-difluoro-phenyl)-urea;

(S)1-[6-Bromo-5-(2-chloro-phenyl)-1,3-dimethyl-2-oxo-
2,3-dihydro-1H-benzo[e][1,4]-diazepin-7-yl]-3-(2-hydroxy-
1-hydroxymethyl-1-methyl-ethyl)-urea;

15 3-(4,5-Diphenyl-1H-imidazol-2-ylsulfanylmethyl)-1-methyl-
piperidine;

2-(5,5-Dimethyl-[1,3]dioxan-2-yl)-4,5-diphenyl-1H-imidazole;

2,2-Dimethyl-5-[3-(1-methyl-1H-imidazol-2-yl)-2-propyl-
chroman-6-yloxy]-pentanoic acid ethyl ester;

N-(4-Hexadecylamino-benzoyl)-4-methyl-benzenesulfonamide;

20 2-(4-Chloro-phenyl)-6-cyclohexyl-4-(2-oxo-2-phenyl-ethyl)-
6,7-dihydro-4H-1,4,6,8a-tetraaza-s-indacene-5,8-diol;

[2-(3-tert-Butyl-4-hydroxy-naphthalen-1-yl)-1-(diethoxy-
phosphoryl)-vinyl]-phosphonic acid diethyl ester;

25 5-[1-(acetyloxy)-3-methylbutyl]-2'-(hydroxymethyl)-4-methoxy-
4'-methylspiro[benzofuran-2(3H),1'-cyclohexa-2',4'-diene]-3,6'-diol;

5-[1-(acetyloxy)-3-methylbutyl]-4-methoxy-4'-methyl-
3,6-dioxospiro[benzofuran-2(3H),1'-cyclohexa-2',4'-diene]-2'-
carboxaldehyde;

30 (3 α ,4 α ,22 α ,24 α)-3-hydroxy-22-[(1-oxooctadecyl)oxy]-24-norolean-
12-en-29-oic acid;

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1-[5-(4,5-Diphenyl-1H-imidazole-2-sulfinyl)-pentyl]-3,5-dimethyl-1H-pyrazole;

N-butyl-3-[[[(4-decyloxyphenyl)carbonyl]-amino]-4-(methylthio)-benzamide;

5 *N,N'*-1,11-Undecanediylbis[2,3-dihydro-2-methyl]-1*H*-indole-1-carboxamide;

N,N'-[1,3-Phenylenebis(methylene)]bis[*N*-cycloheptyl-*N'*-[4-(dimethylamino)phenyl]]-urea; and

10 1-[5-[(*S*)-(4,5-Diphenyl-1*H*-imidazol-2-yl)sulfinyl]pentyl]-4,5-dihydro-3,5-dimethyl-1*H*-pyrazole.

FIG. 1

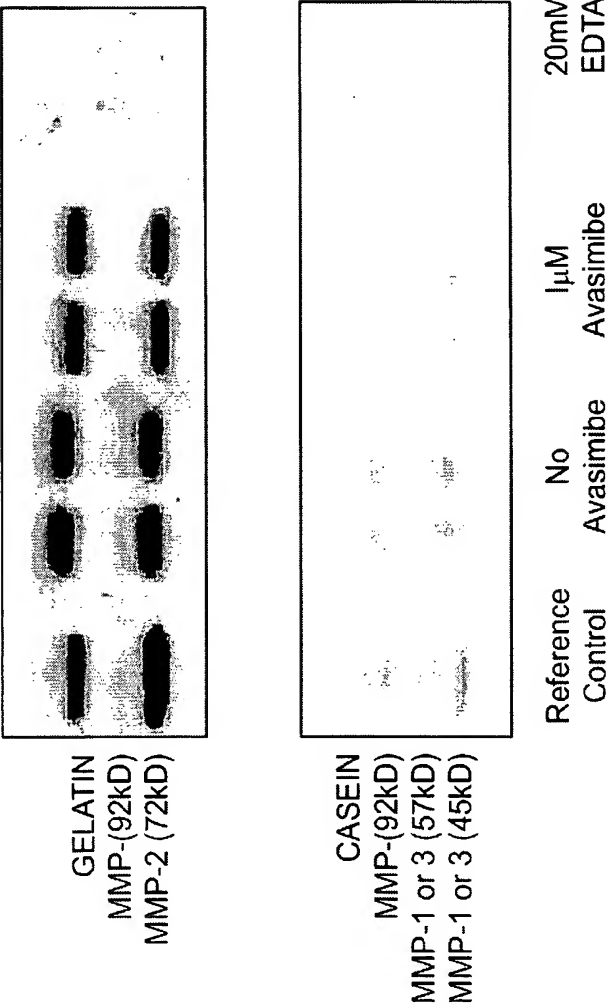


FIG. 2

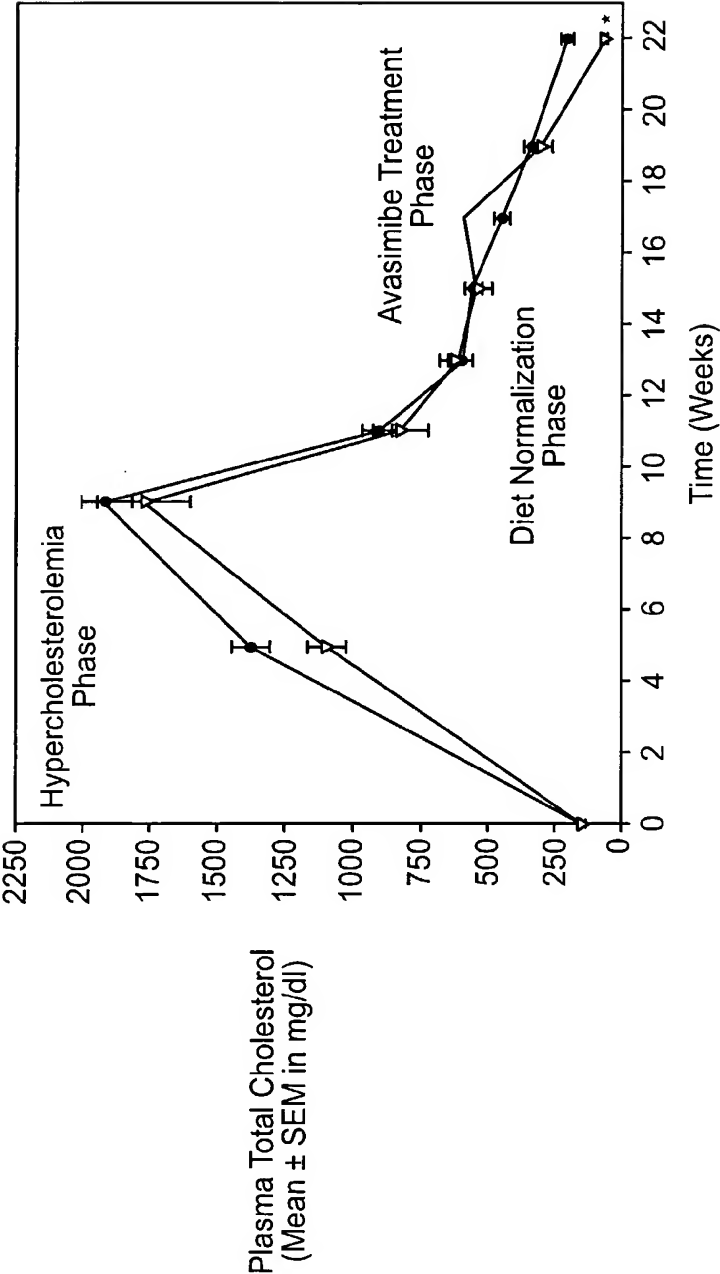


FIG. 3

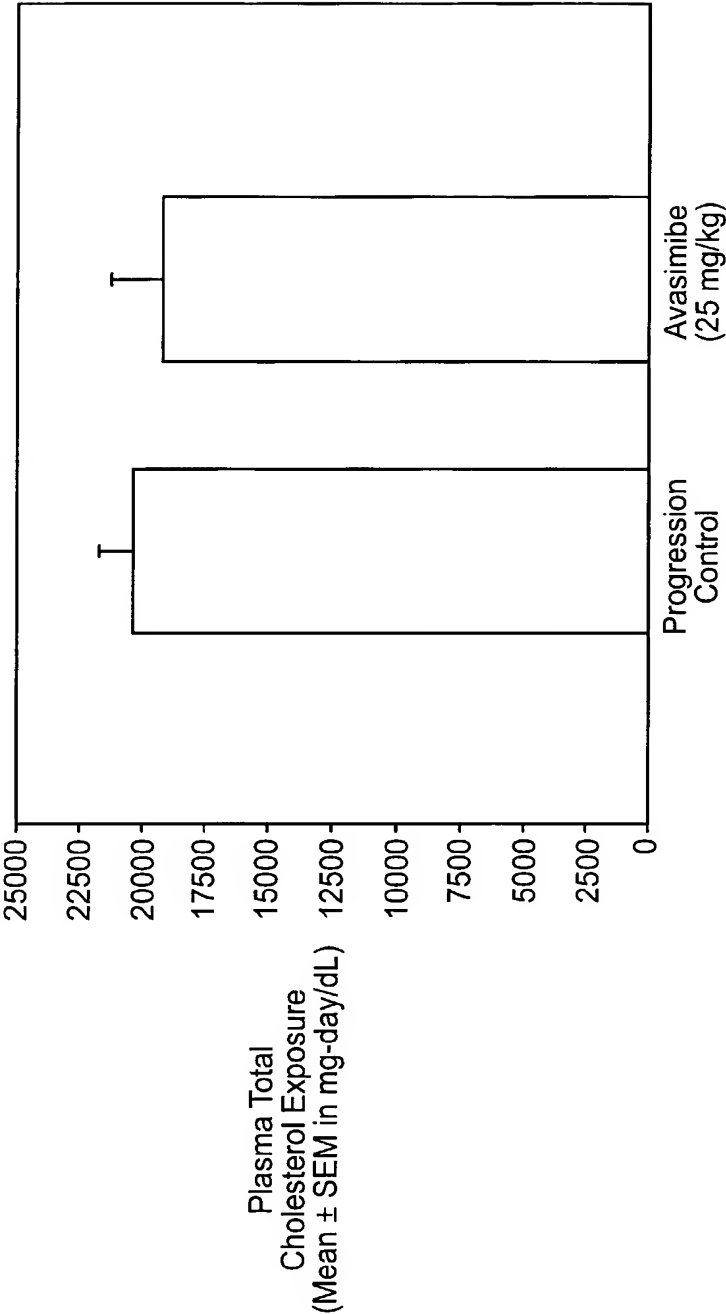
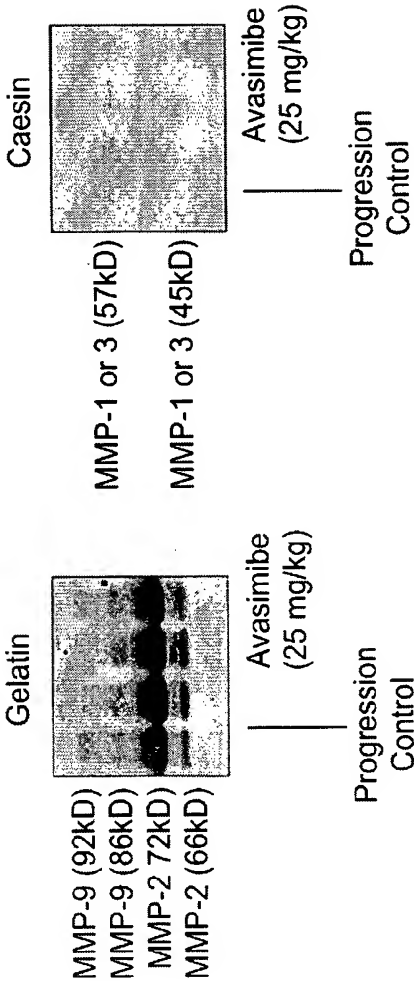


FIG. 4 FIG. 5



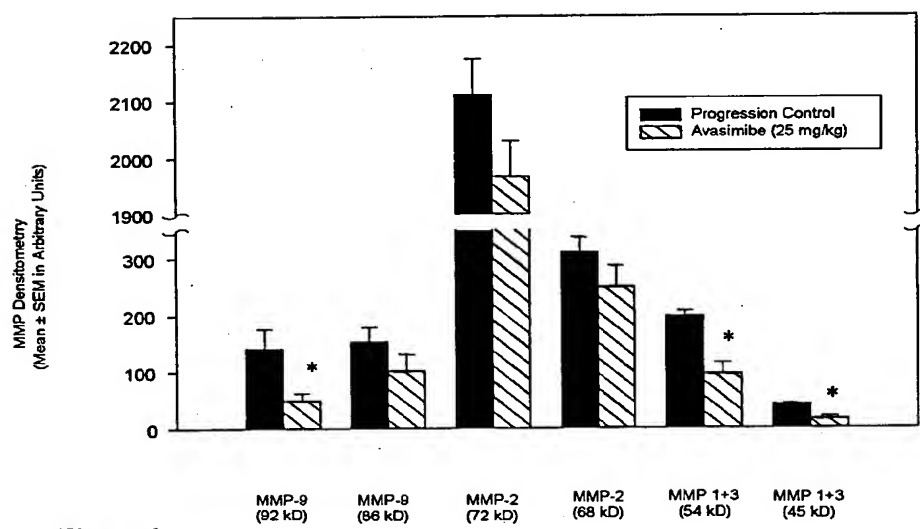


Figure 6

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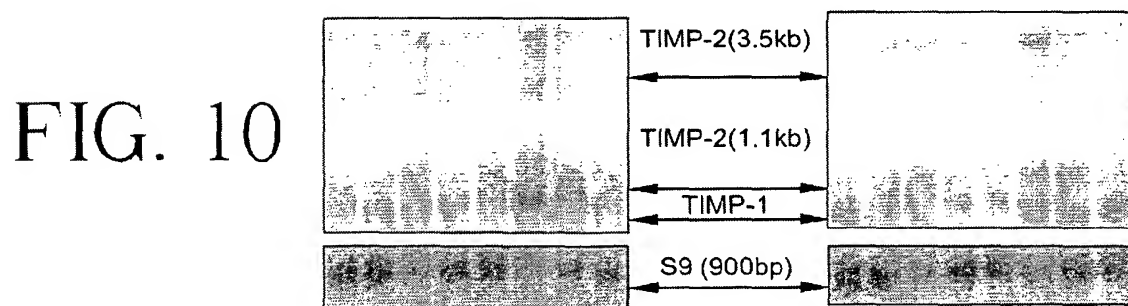
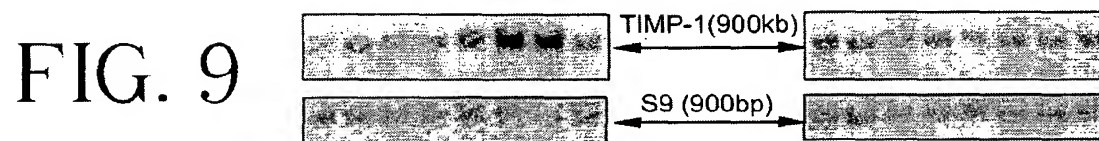
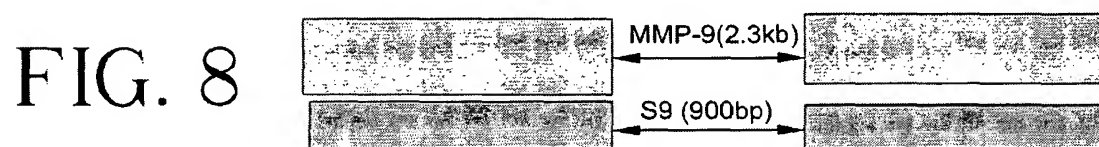
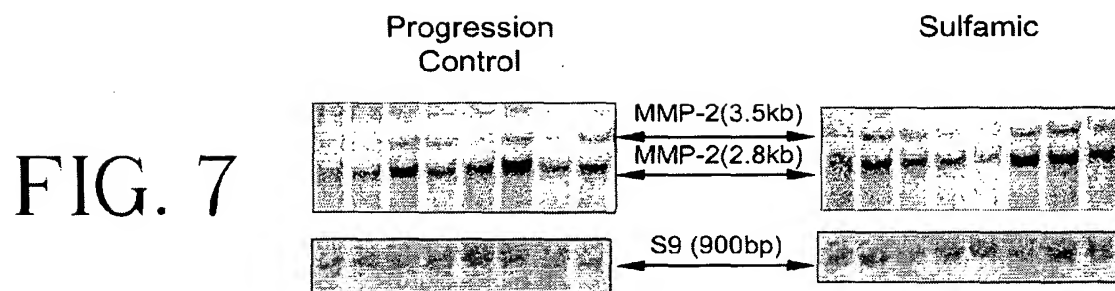


FIG. 11

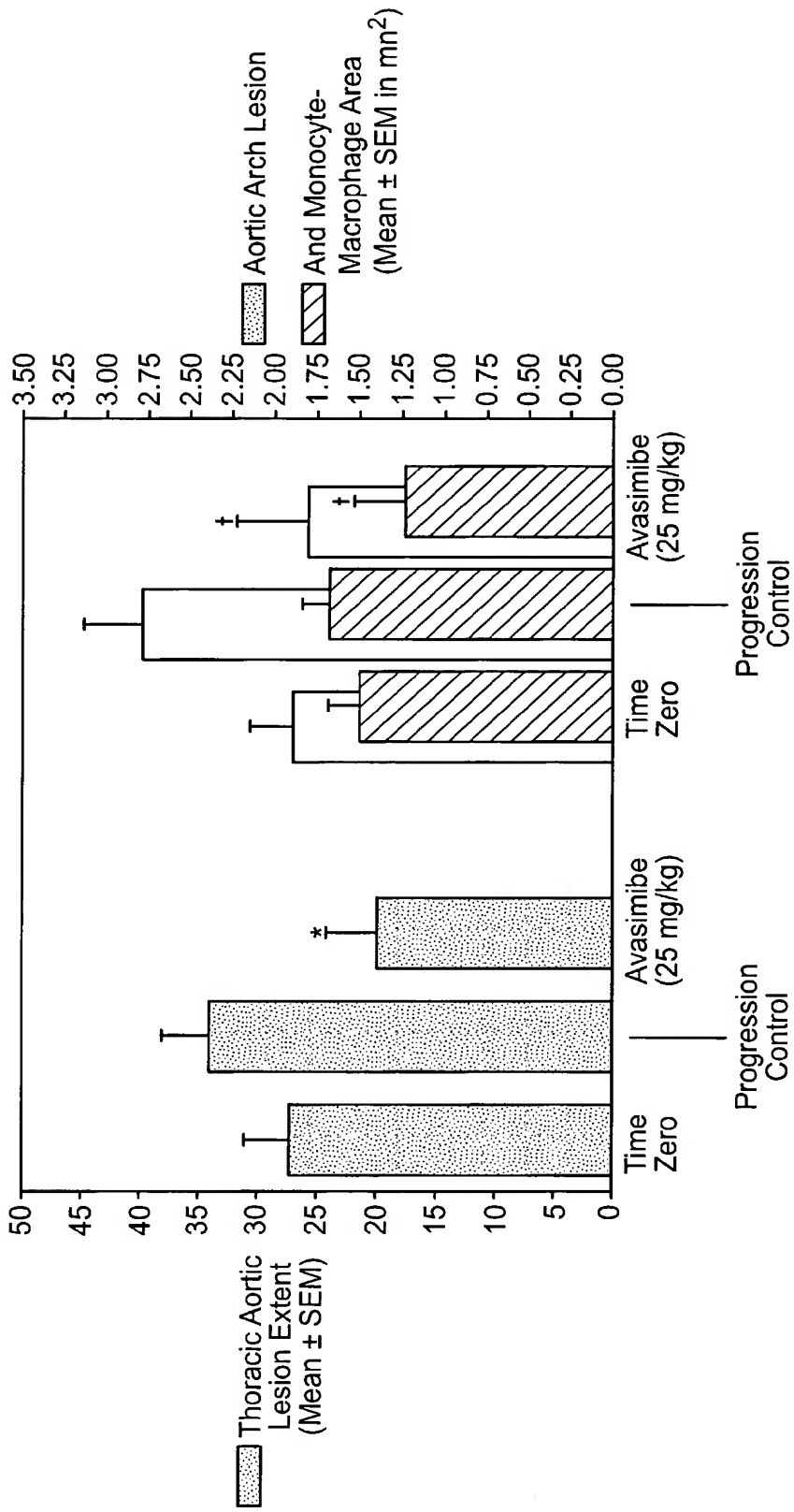
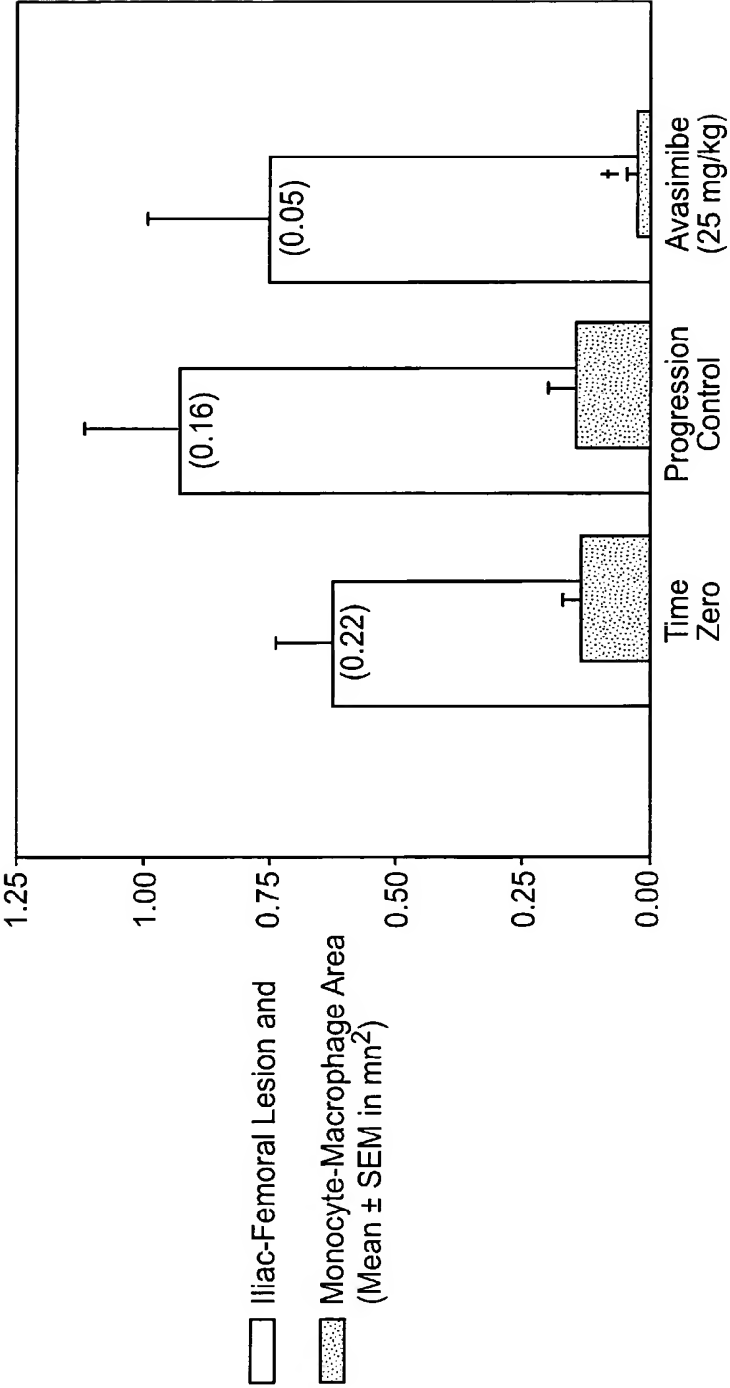


FIG. 12



INTERNATIONAL SEARCH REPORT

Inter: Application No
PCT/US 00/28705

A. CLASSIFICATION OF SUBJECT MATTER

IPC 7 A61K31/00 A61K31/255 A61K31/27 A61K31/18 A61K31/41
A61P9/10

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 7 A61K A61P

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

EPO-Internal, CHEM ABS Data, BIOSIS, MEDLINE, EMBASE, SCISEARCH

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
P, X	WO 00 04892 A (BOCAN THOMAS MICHAEL ANDREW ; WARNER LAMBERT CO (US)) 3 February 2000 (2000-02-03) abstract page 2, line 12 -page 3, line 11 page 148, line 20 -page 159, line 24; claims 1,2,18-31	1-5, 9-13, 17-21, 25-29
P, X	BOCAN, THOMAS M. A. ET AL: "The ACAT inhibitor avasimibe reduces macrophages and matrix metalloproteinase expression in atherosclerotic lesions of hypercholesterolemic rabbits" ARTERIOSCLER., THROMB., VASC. BIOL. (2000), 20(1), 70-79 , XP000997385 the whole document	1-5, 9-13, 17-21, 25-29



Further documents are listed in the continuation of box C.



Patent family members are listed in annex.

* Special categories of cited documents :

- *A* document defining the general state of the art which is not considered to be of particular relevance
- *E* earlier document but published on or after the international filing date
- *L* document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
- *O* document referring to an oral disclosure, use, exhibition or other means
- *P* document published prior to the international filing date but later than the priority date claimed

- *T* later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
- *X* document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
- *Y* document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.
- *G* document member of the same patent family

Date of the actual completion of the international search

3 April 2001

Date of mailing of the international search report

02/05/2001

Name and mailing address of the ISA

European Patent Office, P.B. 5818 Patentlaan 2
NL - 2280 HV Rijswijk
Tel. (+31-70) 340-2040, Tx. 31 651 epo nl,
Fax: (+31-70) 340-3016

Authorized officer

Hoff, P

INTERNATIONAL SEARCH REPORT

International Application No

PCT/US 00/28705

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	JONES, RICHARD: "Avasimibe (Parke-Davis)" CURR. OPIN. CARDIOVASC., PULM. RENAL INVEST. DRUGS (1999), 1(2), 263-269 , 6 October 1999 (1999-10-06), XP000997184 the whole document ---	1-5, 9-13, 17-21, 25-29
X	BOCAN, THOMAS M. A. ET AL: "Might ACAT inhibitors promote development of a stable plaque morphology." CIRCULATION, (10/21/97, 1997) VOL. 96, NO. 8 SUPPL., PP. I491. MEETING INFO.: 70TH SCIENTIFIC SESSIONS OF THE AMERICAN HEART ASSOCIATION ORLANDO, FLORIDA, USA NOVEMBER 9-12, 1997 , XP000997158 the whole document ---	1-5, 9-13, 17-21, 25-29
X	BOCAN, THOMAS M. A. ET AL: "Coadministration of the ACAT inhibitor, CI-1011, and simvastatin induces atherosclerotic lesion regression." CIRCULATION, (OCT. 27, 1998) VOL. 98, NO. 17 SUPPL., PP. I310. MEETING INFO.: 71ST SCIENTIFIC SESSIONS OF THE AMERICAN HEART ASSOCIATION DALLAS, TEXAS, USA NOVEMBER 8-11, 1998 THE AMERICAN HEART ASSOCIATION. , XP000997159 the whole document ---	1-5, 9-13, 17-21, 25-29
X	LAITINEN, LEENA ET AL: "The ACAT inhibitor, CI-1011 is effective in the prevention and regression of atherogenesis in hamsters." FASEB JOURNAL, (1996) VOL. 10, NO. 3, PP. A511. MEETING INFO.: EXPERIMENTAL BIOLOGY 96, PART II WASHINGTON, D.C., USA APRIL 14-17, 1996 , XP000990578 the whole document ---	1-5, 9-13, 17-21, 25-29
X	NICOLOSI, ROBERT J. ET AL: "The ACAT inhibitor, CI-1011 is effective in the prevention and regression of aortic fatty streak area in hamsters" ATHEROSCLEROSIS (SHANNON, IREL.) (1998), 137(1), 77-85 , XP000997273 the whole document --- -/--	1-5, 9-13, 17-21, 25-29

INTERNATIONAL SEARCH REPORT

Intern Application No

PCT/US 00/28705

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 97 16184 A (WARNER LAMBERT CO ;BOCAN THOMAS M A (US)) 9 May 1997 (1997-05-09) page A page 2, line 7 -page 3, line 20 page 5, line 34 -page 12, line 32; claims 18-25 ---	1-5, 9-13, 17-21, 25-29
X	WO 94 26702 A (WARNER LAMBERT CO) 24 November 1994 (1994-11-24) abstract page 7, line 17 - line 25; claims ---	1-5, 9-13, 17-21, 25-29
X	WO 92 07826 A (WARNER LAMBERT CO) 14 May 1992 (1992-05-14) abstract page 13, line 20 - line 28; claims; examples ---	1-5, 9-13, 17-21, 25-29
X	T. M. A. BOCAN ET AL.: "Comparaison of CI-976, an ACAT Inhibitor and Selected Lipid-Lowering Agents for Antiatherosclerosis Activity in Iliac-Femoral and Thoracic Aortic Lesions" ARTERIOSCLEROSIS AND THROMBOSIS, vol. 11, 1991, pages 1830-1843, XP000992580 the whole document ---	1,9,17, 25
X	FERGUSON, ERIKA ET AL: "CI-976, an ACAT inhibitor, decreases monocyte adhesion to aortic endothelial cells." FASEB JOURNAL, (1993) VOL. 7, NO. 3-4, PP. A792. MEETING INFO.: MEETING OF THE FEDERATION OF AMERICAN SOCIETIES FOR EXPERIMENTAL BIOLOGY ON EXPERIMENTAL BIOLOGY '93 NEW ORLEANS, LOUISIANA, USA MARCH 28-APRIL 1, 1993 , XP000990562 the whole document ---	1,9,17, 25
	--- -/--	

INTERNATIONAL SEARCH REPORT

Inter: Application No

PCT/US 00/28705

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	BOCAN, THOMAS M. A. (1) ET AL: "HMG-CoA reductase and ACAT inhibits act synergistically to lower plasma cholesterol and limit atherosclerotic lesion development in the cholesterol-fed rabbit." ATHEROSCLEROSIS, (JULY, 1998) VOL. 139, NO. 1, PP. 21-30. , XP000992556 the whole document ----	1,9,17, 25
X	GB 2 280 675 A (ERBA CARLO SPA) 8 February 1995 (1995-02-08) the whole document ----	1,9,17, 25,33
A	WO 97 05868 A (WARNER LAMBERT CO ;KRAUSE BRIAN ROBERT (US)) 20 February 1997 (1997-02-20) abstract; claims; examples -----	1-5, 9-13, 17-21, 25-29, 33-37

INTERNATIONAL SEARCH REPORT

International Application No. PCT/US 00 28705

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

Continuation of Box I.2

Claims Nos.: 6-8,14-16,22-24,30-32,38-42

Present claims 1,9,17,25,33 relate to a compound defined by reference to a desirable characteristic or property, namely "ACAT inhibitor".

The claims cover all compounds having this characteristic or property, whereas the application provides support within the meaning of Article 6 PCT and disclosure within the meaning of Article 5 PCT for only a very limited number of such compounds. In the present case, the claims so lack support, and the application so lacks disclosure, that a meaningful search over the whole of the claimed scope is impossible. Independent of the above reasoning, the claims also lack clarity (Article 6 PCT). An attempt is made to define the compound by reference to its pharmacological profile. Again, this lack of clarity in the present case is such as to render a meaningful search over the whole of the claimed scope impossible.

Furthermore, the application includes no example or evidence substantiating the therapeutic effect of the compounds mentioned in claims 6-8,14-16,22-24,30-32,38-42 underlying the present invention. Nor is the subject-matter of said claims directly related to the experimental data presented in the application.

Consequently, claims 6-8,14-16,22-24,30-32,38-42 have not been searched.

The search has thus been carried out for those parts of the claims which appear to be clear, supported and disclosed, namely those parts relating to the compounds structurally identified in claims 2-5.

Claims searched completely: 2-5,10-13, 18-21, 26-29,34-37

Claims searched incompletely: 1,9,17,25,33

Claims not searched: 6-8,14-16,22-24,30-32,38-42

The applicant's attention is drawn to the fact that claims, or parts of claims, relating to inventions in respect of which no international search report has been established need not be the subject of an international preliminary examination (Rule 66.1(e) PCT). The applicant is advised that the EPO policy when acting as an International Preliminary Examining Authority is normally not to carry out a preliminary examination on matter which has not been searched. This is the case irrespective of whether or not the claims are amended following receipt of the search report or during any Chapter II procedure.

INTERNATIONAL SEARCH REPORT
 information on patent family members

Inter Application No
 PCT/US 00/28705

Patent document cited in search report		Publication date	Patent family member(s)	Publication date
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